A different perspective on bipolar disorder?

Regeer, Eline Janet

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Epidemiology, consequences, concept, and recognition of bipolar spectrum disorder in the general population

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Stellingen behorend bij het proefschrift

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1. Een diagnose bipolaire stoornis vastgesteld met een gestructureerd interview afgenomen door getrainde leken (CIDI) komt matig overeen met een klinische diagnose bipolaire stoornis vastgesteld met de SCID. *(dit proefschrift)*

2. Op basis van een klinisch interview (SCID) is in de algemene bevolking de lifetime prevalentie voor bipolaire spectrum stoornissen 5.2%. *(dit proefschrift)*

3. Subsyndromale hypomanie en subsyndromale depressie zijn een risicofactor voor het ontwikkelen van een bipolaire stoornis. *(dit proefschrift)*

4. Mensen met een bipolaire spectrum stoornis rapporteren slechter te functioneren (meer ziekteverzuim, verminderde productiviteit op hun werk) en een lagere kwaliteit van leven dan mensen in de algemene bevolking. *(dit proefschrift)*

Lnwr Syndicate!

5. De bipolaire spectrum stoornis wordt door zowel de huisarts als door de GGZ slecht herkend. *(dit proefschrift)*

6. Erkenning en acceptatie van de bipolaire spectrum stoornis door de patiënt is één van de belangrijkste factoren voor het ontvangen van adequate behandeling. *(dit proefschrift)*

7. Na het stellen van de diagnose bipolaire stoornis is aandacht voor acceptatie van de ziekte en kennis over de stoornis belangrijk om therapietrouw te bevorderen.

8. Naast het huidige categoriale classificatiesysteem is het nuttig psychopathologie ook aan de hand van dimensies (depressie, manie, psychose, episode frequentie) te beschrijven.

9. Aandacht voor het verhaal en het leven van de patiënt draagt in belangrijke mate bij aan een goede behandelrelatie.

10. Een goede behandelrelatie is de beste voorspeller voor medicatietrouw en het in zorg blijven van de patiënt.

11. Het opbouwen van een goede behandelrelatie is een van de meest interessante aspecten van het werk van de psychiater.

12. Problemen bestaan niet, alleen oplossingen. *(R.W. Fischer)*

13. Een stoornis is pas een stoornis als je je eraan stoort. *(Rafaeline)*

Eline Regeer, november 2007

The studies described in chapter 2, 3 and 6 were designed and performed in collaboration with the Netherlands Institute of Mental Health and Addiction (Trimbos-instituut) and the Institute for Medical Technology Assessment, Erasmus Medical Center, Rotterdam, The Netherlands.

The studies described in chapter 4 and 5 were designed and performed in collaboration with the Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University and the Institute of Mental Health and Addiction (Trimbos-instituut), The Netherlands.

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Proefschrift

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aan de Rijksuniversiteit Groningen
op gezag van de
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door

Eline Janet Regeer
geboren op 4 juli 1970
te Moerkapelle

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Contents

CHAPTER 1

GENERAL INTRODUCTION

General introduction

Because my illness seemed at first simply to be an extension of myself—that is to say, of my ordinarily changeable moods, energies, and enthusiasm—I perhaps gave it at times much too quarter. And, because I thought I ought to be able to handle my increasingly violent mood swings by myself, for the first ten years I did not seek any kind of treatment. Even after my condition became a medical emergency, I still intermittently resisted the medications that both my training and clinical research expertise told me were the only sensible way to deal with the illness I had.

The major clinical problem in treating manic-depressive illness is not that there are not effective medications—there are—but that patients often refuse to take them. Worse yet, because of a lack of information, poor medical advice, stigma, or fear of personal and professional reprisals, they do not seek treatment all.

(Cited from: *An unquiet mind; a memoir of moods and madness* by Kay Redfield Jamison, 1995)

Kay Redfield Jamison, Professor of Psychiatry at the Johns Hopkins University School of Medicine suffered from bipolar disorder since she was 17 years old. As described above, it took her about 10 years to seek help, illustrating one of the difficulties related to the treatment of patients with bipolar disorder. Aside from the delay in help-seeking by patients, bipolar disorder is poorly recognized and often remains undiagnosed not only in general practice but also in mental health care. Moreover, bipolar disorder is often misdiagnosed as, for instance, (unipolar) depressive disorder. Consequently, many studies have reported long delays between the onset of the first symptoms of the illness and receiving the correct diagnosis and treatment. Most of these studies however were done in clinical samples, which means that the patients included suffered from a more severe form of bipolar disorder and had sought treatment. Hence, little is known about the effect of the above mentioned factors in the general population, and consequently little is known of factors influencing help-seeking and receiving adequate treatment. Another interesting point is that the current concept of bipolar disorder is mainly based on studies in clinical samples, and one can question whether this concept reflects the true nature of mood dysregulation. Research in the general population offers a unique opportunity to study a wider range of expressions of mood disorder, its consequences, diagnostic process and treatment history in a naturalistic setting not influenced and biased by help-seeking behaviour.

In this thesis we report on four studies into the nature, prevalence and consequences of bipolar disorder as well as a study into factors influencing help-seeking and receiving treatment in the Dutch general population using data and respondents taken from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). In this introductory chapter a short history of the concept of bipolar disorder is given. Next, classification and methodological issues on bipolar disorder are discussed and prevalence rates from various studies are presented. Finally, the studies included in this thesis as well as the design of and some previous results of NEMESIS are described.

History of the concept of bipolar disorder

The first description of mania and melancholia in the same person over time was given by the Roman physician Aretaeus of Cappadocia in the 2nd century AD. He proposed that mania was an end stage of melancholia. In 1854, a disorder with alternating mania, melancholia and a symptom-free interval was described by Falret as *la Folie circulaire* and by Baillarger as *la folie à double forme*. In 1882, Kalmbaum described milder forms of this periodic illness: cyclothymia and dysthymia (Goodwin & Jamison, 2007).

The term manic-depressive insanity (*das manisch-depressive Irresein*) was originally introduced by Kraepelin in 1899 to distinguish less severe psychoses from *Dementia praecox* (schizophrenia). Kraepelin's terminology included both bipolar and unipolar mood disorders because of their similarity in core symptoms, presence of a family history of the same disease, the pattern of recurrence with period of remission and exacerbation, and a comparatively benign outcome without significant deterioration. This unitary concept of mood disorders lasted until 1953 when Kleist published his diagnostic classification in which he made the distinction between unipolar and bipolar disorder, later confirmed by Angst (1966) and by Perris (1966) based on factors discriminating both disorders from each other, such as course of illness and occurrence within families. Dunner and colleagues (1976) proposed the distinction between bipolar I and bipolar II disorder on the basis of hospitalization for depression and hypomanic periods that did not require hospitalization. Krauthammer and Klerman (1978) pointed out that mania itself is not a discrete disorder and can arise not only in bipolar disorder but also in a variety of neuromedical and toxicological conditions, in which case it is called secondary mania.

DSM criteria and subtypes of mood disorders

Bipolar disorder is a mood disorder characterized by episodes of mania, hypomania and depression. The severity ranges from mild cyclothymia to severe bipolar disorder with psychotic features. Over time the diagnostic criteria of the American Diagnostic and Statistical Manual for Mental Disorders (DSM) for bipolar disorder have changed. Table 1.1 describes the various episodes that can occur in patients with bipolar disorder. Differences in DMS-III (APA, 1980), DSM-III-R (APA, 1987) and DSM-IV (APA, 1994) criteria are given. Table 1.2 describes the subtypes of mood disorders in DSM-III, DSM-III-R and DSM-IV.

In DSM-III (APA, 1980) the bipolar mood disorders included bipolar disorder, cyclothymic disorder (before DSM-III cyclothymia was classified as a personality disorder), and atypical bipolar disorder. Bipolar disorder required a week or more of manic symptoms or hospitalization. Atypical bipolar disorder included all bipolar disorders that did not specifically meet diagnostic criteria and particularly included patients who are currently described as bipolar II disorder (depression and hypomania). So in DSM-III bipolar disorder reflects what currently is described as bipolar I disorder. In DMS-III-R (APA, 1987) the definitions slightly changed. Bipolar mood disorders included bipolar disorder, cyclothymia and bipolar disorder not otherwise specified (NOS), which also included bipolar II disorder. The duration criterion for a manic episode was deleted. In DMS-IV (APA, 1994) the duration criteria for a manic episode was reinstated. Bipolar II disorder became a separate classification supported by data on clinical features, family history, course and outcome and biological factors (Dunner, 1993). The duration of 4 days or more as a minimal duration was arbitrarily chosen. Hypomania is the only major DSM-IV diagnosis in which the criterion of social and occupational dysfunction is not required; on the contrary, significant social and occupational dysfunction must be ruled out. So hypomania is mainly distinguished from mania based on function rather than symptoms. DSM-IV bipolar disorder further includes cyclothymia (recurring hypomanic episodes and mild depressions for more than 2 years) and bipolar disorder NOS (very rapid alternation (within days) between manic and depressive symptoms that do not meet minimal duration criteria for a manic or a major depressive episode, or recurrent hypomanic episodes without intercurrent depressive symptoms). A separate category is included for mood disorder due to a general medical condition or substance use specified with depressive, manic or mixed characteristics. By creating this separate category, antidepressant-induced (hypo)mania was excluded from the DSM-IV diagnosis of bipolar disorder.

Table 1.1 Diagnostic criteria for mood episodes according to DSM-III, DSM-III-R, and DSM-IV

Major depressive episode*
A. Depressed mood or loss of interest during most of the day for at least 2 weeks
B. During the same period 4 or more of the following features:
Change of appetite or weight
Insomnia or hypersomnia
Psychomotor retardation or agitation
Fatigue or loss of energy
Feelings of worthlessness or guilt
Impaired thinking or concentration, or indecisiveness
Thoughts of death, or suicidal ideation or plans

Symptoms cause significant distress or impairment in social, occupational, or other important areas of functioning

Manic episode*
A. Elevated, expansive or irritable mood
B. During the same period of mood disturbance at least 3 or more (4 if only irritable mood) of the following symptoms:
Inflated self-esteem or grandiosity
Decreased need for sleep
More talkative or pressure of speech
Flight of ideas or racing thoughts
Distractibility
Increased goal-directed activity or psychomotor agitation
Excessive involvement in activities with painful consequences

Symptoms last at least 1 week (or any time if hospitalization is needed) (DSM-III and DSM-IV)
Symptoms last a distinct period (DSM-III-R)

Symptoms cause significant impairment in social or occupational functioning or require hospitalization (DSM-III-R and DSM-IV)

Hypomanic episode*
Criterion A and B as in manic episode

In DMS-III-R not specified as a separate episode

Symptoms last at least 4 days and are associated with a change in normal functioning, but do not cause marked impairment in social or occupational functioning (DSM-IV)

Mixed episode*
Criteria are met for both a manic and a major depressive disorder during at least 1 week

Symptoms cause significant impairment in social or occupational functioning or require hospitalization (DSM-IV)

In DMS-III and DMS-III-R not specified as a separate episode

* For all episodes the additional requirement must be fulfilled that the symptoms are not due to the direct physiological effect of a substance (drugs abuse, medication) or general medical condition.

Table 1.2 Subtypes of mood disorders according to DSM-III, DSM-III-R, and DSM-IV

DSM-III	*DSM-III-R*	*DSM-IV*
Bipolar disorder • Mixed • Manic • Depressed	Bipolar disorders • Bipolar disorder mixed, manic, depressed • Cyclothymia • Bipolar disorder NOS	Bipolar disorders • Bipolar I disorder single manic episode last episode: hypomanic, manic, mixed, depressive • Bipolar II disorder • Cyclothymic disorder • Bipolar disorder NOS
Major depression • Single episode • Recurrent	Depressive disorders • Major depression single, recurrent • Dysthymia • Depressive disorder NOS	Depressive disorders • Major depressive disorder single, recurrent • Dysthymic disorder • Depressive disorder NOS
Other specific affective disorders • Cyclothymic disorder • Dysthymic disorder		Other mood disorder • Mood disorder due to general medical condition or substance use • Mood disorder NOS
Atypical affective disorders • Atypical bipolar disorder • Atypical depression		

NOS = Not otherwise specified

Bipolar spectrum disorder

Bipolar disorder is probably broader than what is included in the DSM-IV and ranges from psychotic and non-psychotic bipolar I disorders to attenuated forms that manifest themselves at the level of disordered (cyclothymic or hyperthymic) temperament (Akiskal, 2002). Angst et al. (2003*a*) included the so-called 'soft' bipolar spectrum, which represents the softest expression of bipolarity occupying an intermediate position between bipolar disorder and normality. Epidemiological studies (Akiskal, 2002; Angst et al., 2003*a*; Judd & Akiskal, 2003; Akiskal et al., 2006*a*; Akiskal et al., 2006*b*) are in support of widening the boundaries of the bipolar spectrum to include bipolar I disorder (mania with or without psychoses), bipolar II disorder (hypomania with a modal duration of 2 days or brief hypomania as short as one day), and bipolar III disorder (antidepressant-induced hypomania).

To further emphasize the concept of a continuum within the broad spectrum, Akiskal (2002) and Akiskal and Pinto (1999) proposed the following intermediary forms:

- bipolar 1/2: schizobipolar disorder
- bipolar 1 1/2: protracted hypomania
- bipolar II 1/2: cyclothymic temperament (constant mood swings) and major depression
- bipolar III 1/2: prominent mood swings in association with substance or alcohol abuse
- bipolar IV: hyperthymic temperament (lifelong traits of cheerful disposition, high drive and energy, overconfidence) and major depression.

In addition, Akiskal (2002) argued for inclusion of borderline personality disorder in the bipolar spectrum. There is an extensive overlap between bipolar II disorder, cyclothymia and borderline personality disorder, including mood lability, impulsivity, disinhibition on antidepressants, and familial bipolarity.

Finally, Ghaemi and Goodwin (2002) lumped all the non-type I or type II subgroups of bipolar disorder into one label (bipolar spectrum disorder) and suggested specific diagnostic guidelines for bipolar spectrum disorder (see table 1.3). They give greater weight to the presence of family history of bipolar disorder and antidepressant-induced manic symptoms following a prospective study by Akiskal and colleagues (1983) which showed that treatment induced hypomania was 100% specific and family history was 98% specific for a bipolar outcome among depressive patients with no past (hypo)manic episodes.

Table 1.3 Proposed definition of bipolar spectrum disorder by Ghaemi and Goodwin (2002)

A. At least one major depressive episode
B. No spontaneous hypomanic or manic episodes
C. Either of the following, plus at least 2 items from criterion D, or both of the following plus 1 item from criterion D:
    1. A family history of bipolar disorder in a first degree relative
    2. antidepressant-induced mania or hypomania
D. If no items from criterion C are presents, 6 of he following 9 criteria are needed:
    1. Hyperthymic personality (at baseline, non depressed state)
    2. Recurrent major depressive episodes (>3)
    3. Brief major depressive episodes (on average < 3 months)
    4. Atypical depressive symptoms (DSM-IV criteria)
    5. Psychotic major depressive episodes
    6. Early age of onset of major depressive episode (< age 25)
    7. Postpartum depression
    8. Antidepressant "wear-off" (acute but no prophylactic response)
    9. Lack of response to three or more antidepressant treatment trials

Methodological difficulties in the establishment of the prevalence of bipolar disorder

It has been suggested that the most suitable place to study the epidemiology of bipolar disorder is in the general population since a substantial portion of the people with a bipolar disorder do not receive mental health care. Therefore, establishment of prevalence rates based on clinical samples will underestimate the prevalence of bipolar disorder and give a distorted view of the expression of bipolar disorder. However, to determine the prevalence of a relatively rare disease in the general population, a large number of participants is necessary. From the 80s up to now, population surveys on mental disorders with large numbers of respondents and similar methodology have been carried out in various countries. Although these surveys made it possible to estimate the prevalence of bipolar disorder more accurately, there are still some methodological problems (Bebbington & Ramana, 1995).

The first problem is the definition of bipolar disorder. Are only bipolar I disorder and bipolar II disorder included or are the milder expression of bipolar disorder included as well? What is the minimal duration of a hypomanic episode and how many and which symptoms need to be present? Do cyclothymia, an antidepressant-induced (hypo)manic episode and the intermediary forms proposed by Akiskal belong to the bipolar spectrum?

Secondly, prevalence rates depend on the classification system used as shown by a study among patients with psychosis according to the Research Diagnostic Criteria (RDC, Spitzer et al., 1978). Of the 709 included patients, 4.9% fulfilled the RDC criteria for bipolar disorder. When the DMS-III-R criteria or the criteria of the International Classification of Diseases (ICD-10, WHO, 1992) were applied, 21.7% and 9.5% of the patients were diagnosed with a bipolar disorder, respectively (van Os et al., 1999). In older studies often only the prevalence of bipolar I disorder is determined, and DSM-III or DSM-III-R classification is used, which makes comparison with recent research difficult due to the fact that recent research uses DSM-IV criteria for bipolar disorder. As described above, the DSM-IV classification of bipolar disorder includes different subtypes of bipolar disorder and minimal duration criterion of manic and hypomanic episode.

Thirdly, the prevalence rates are influenced by the diagnostic instrument used: a structured interview as the Composite International Diagnostic Interview (CIDI, Robins et al., 1988) administered by trained lay interviewers or a clinical instrument as the Structured Clinical Interview for DSM-IV disorders (SCID, Spitzer et al., 1992). A normal happy mood is difficult to distinguish from a pathological elevated mood without considerable clinical experience. Therefore, a structured interview performed by a lay interviewer may over estimated hypomanic episodes (Bebbington & Ramana,

1995). Finally, lack of insight into the abnormality of the mood change and recall bias may cause underestimation of (hypo)manic episodes. Despite these limitations an overview of epidemiological studies on the prevalence of bipolar disorder is given.

Epidemiology of bipolar disorder

Prevalence studies

A review of five epidemiological studies published before 1980 mentioned a lifetime prevalence of bipolar disorder of 0.28 to 0.88% (Boyd & Weissman, 1981). However, in the majority of the older epidemiological studies, the diagnostic procedures were vague and bipolar disorder was not adequately distinguished from unipolar disorder. In the majority of these studies the Kraepelin definition of manic-depressive illness was used. Krauthammer and Klerman (1979) estimated that between 15% and 32% of the hospitalized manic-depressives would meet the DSM-III criteria for bipolar disorder. Over time many epidemiological studies were done in which instruments based on standardized diagnostic criteria were used (see table 1.4). First, I will mention some American studies followed by studies from various other western and non-western countries.

The first epidemiological study using a validated instrument was carried out in New Haven among 511 respondents (Weissman & Myers, 1978). The Schedule for Affective Disorders and Schizophrenia (SADS, Endicott & Spitzer, 1978) based on the Research Diagnostic Criteria (RCD, Spitzer et al., 1978) was used. A lifetime prevalence of 0.6% of bipolar I disorder and a lifetime prevalence of 0.6% of bipolar II disorder was found. Another study was performed among 20,861 North-American respondents, the Epidemiological Catchment Area study (Weissman et al., 1991). DSM-III-diagnoses were determined using the Diagnostic Interview Schedule (DIS). The lifetime prevalence for bipolar I disorder was 0.8% (men 0.7%, women 0.9%) and for bipolar II disorder 0.5% (men 0.4%, women 0.5%). The highest lifetime prevalence was found in the age category 33-44 years.

Epidemiological research in the USA continued with the National Comorbidity Survey (NCS), performed among 8098 respondents aged 15-54 years (Kessler et al., 1994). In this study, the CIDI was used to determine DSM-III-R disorders. In general, the prevalence percentages found in the NCS were higher than in the ECA. The lifetime prevalence for a manic episode (bipolar I disorder) was 1.6% (men 1.6%, women 1.7%).

In the National Comorbidity Survey Replication (NCS-R) among 9282 respondents aged 18 year and older, the prevalence of DSM-IV diagnoses was established with the CIDI. A lifetime prevalence of 1.0% and a 12-month prevalence of 0.6% for

bipolar I disorder, and a lifetime prevalence of 1.1% and a 12-month prevalence of 0.8% for bipolar II disorder was found (Merikangas et al., 2007). The lifetime prevalence in the age category 18-29 years was highest (5.9%) and lowest in the age category 60 years and older (1.0%) (Kessler et al., 2005).

The last American study to be mentioned is the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). DSM-IV axis I and II diagnoses were determined by a structured interview developed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). A lifetime prevalence of 3.3% and a 12-month prevalence of 2.0% of bipolar I disorder was found (Grant et al., 2005).

Apart from these mentioned studies in the US, various other studies in western and non-western countries were done. The lifetime prevalence in these studies for bipolar I disorder varied from 0.07% (Taiwan) to 2.2% (Canada) (Hwu et al., 1989; Fogarty et al., 1994; Szadoczky et al., 1998; Wittchen et al., 1998; Angst et al., 2003*b*; Faravelli et al., 2004*a*, Kawakami et al., 2004; Negash et al., 2005; Vicente et al., 2005; Faravelli et al., 2006; Schaffer et al., 2006) and for bipolar II disorder from 0.4% (Germany) to 2.0% (Hungary) (Hwu et al., 1989; Szadoczky et al., 1998; Wittchen et al., 1998; Angst et al., 2003*b*; Faravelli et al., 2004*a*; Faravelli et al., 2006).

In the Netherlands Mental Health Survey and Incidence Study (NEMESIS) among 7076 respondents aged 18-64 years and representative for the Dutch population, a lifetime prevalence of 1.3% for bipolar I disorder and of 0.6% for bipolar disorder NOS was determined by the CIDI/DSM-III-R (ten Have et al., 2002). Bipolar disorder NOS was more common among women in comparison to men (43.6% vs. 15.3%) (ten Have et al., 2002).

The low prevalence of bipolar disorder (0.07%-0.5%) found in various Asian studies (Hwu et al., 1989; Kawakami et al., 2004; Shen et al., 2006), in Ethiopia (Negash et al., 2005) and in the United Arab Emirates (Abou-Saleh et al., 2001) suggests a protective influence of cultural factors, such as traditional cultural retention and consistent cultural support. This is in line with the results in the NESARC study with a lower prevalence of bipolar I disorder among Asian (2.0%) and Hispanic (3.1%) respondents compared to white Americans (3.3%) although a high prevalence was found among Native Americans (5.2%) (Grant et al., 2005). However, these low prevalence rates may also by the result of underreporting due to language problems or other ways of expression of psychiatric symptoms and fear of stigmatization. Other studies found higher incidence and prevalence of bipolar disorder among African-Caribbean, African and Hispanic people (van Os et al., 1996; Lloyd et al., 2005; Breslau et al., 2006) indicating an influence of factors related to migration such as living in an urban environment, adjusting problems, less changes and opportunities. The differences in prevalence rates may also be the result of different genetic influence across the different racial populations.

Not mentioned in table 1.4 but noteworthy is a study among the Amish population because of the culturally and genetically homogeneous study sample (Egeland & Hostetter, 1983). The Amish area conservative group of Protestants living in Pennsylvania who do not drink alcohol or use drugs and who rarely show acts of violence or crime. Of the 8186 Amish aged 15 years or older, 112 suffered from a mental disorder based on consensus diagnosis using the Research Diagnostic Criteria (RCD). Bipolar I or II disorder accounted for 43% of the mental disorders in the sample and unipolar depression for 37%. The prevalence of bipolar disorder and unipolar depression was about 1%, which is much lower than in other studies and may suggest a protective influence of a closed social system and the absence of alcohol and drugs. An interesting finding is that the ratio of unipolar disorder to bipolar disorder is almost 1:1. Other studies found unipolar/bipolar ratios of 4-10:1 (Goodwin & Jamison, 2007). An explanation could be the special attention in this study on hypomanic symptoms. This finding could also be an indication of hidden bipolarity in other research populations and the Amish data may reflect more accurately the bipolar:unipolar ratio (Egeland & Hostetter, 1983; Goodwin & Jamison, 2007).

Bipolar spectrum

When the concept of bipolar disorder is extended to the bipolar spectrum, i.e., including cyclothymia and (hypo)manic syndromes with only some (hypo)manic symptoms or when the duration criterion is not met, prevalence rates rise. Various studies examine the prevalence of the bipolar spectrum (see table 1.4).

The first study to mention is the Zurich Young Cohort study, a 20-year prospective community-based study (Angst et al., 2003*a*; Angst et al., 2003*b*). A cohort of 4547 subjects between 19-20 years old was screened with the Symptom Checklist 90-R. In order to increase the probability of psychiatric syndromes, a sub-sample with high scores on the SCL-90-R was selected for 6 follow-up interviews between 1979-1999. A prevalence of DSM-IV bipolar I disorder of 0.6%, of DSM-IV bipolar II disorder of 1.7% and of DSM-IV major depressive disorder of 20.7% was found. When a broader definition of hypomania is applied, i.e., "a syndrome (no minimum duration) characterized by the presence of 1. overactivity, euphoria or irritability; 2. have themselves experienced problems or received comments from others that something must be wrong with them; 3. presence of at least three out of seven signs or symptoms of DSM-IV hypomania", then 5.3% of the subjects meet the criteria for a bipolar II disorder (hard criteria). An additional 5.7% experienced hypomanic symptoms without consequences (soft criteria). Using a broader definition of hypomania does not produce higher prevalence rates of mood disorders but merely reduces the prevalence of major depressive disorders (Angst et al., 2003*a*; Angst et al., 2003*b*).

Table 1.4 Prevalence of bipolar disorder in the general population

Study	Population (response)	Instrument Classification	Diagnosis	Lifetime			12-month			1-month		
				M	F	total	M	F	total	M	F	total
USA: New Haven 1975-1976 (Weissman et al., 1978)	511 (72%) > 25 year	SADS-RCD DSM-III	Bipolar I disorder Bipolar II disorder	- -	- -	0.6 0.6	- -	- -	- -	- -	- -	- -
USA: ECA 1980-1984 (Weissman et al., 1991)	18000 (75-80%) general population New Haven, Baltimore, St Louis, Piedmont, Los Angeles > 17 year	DIS DSM-III	Bipolar I disorder Bipolar II disorder	0.7 0.4	0.9 0.5	0.8 0.5	0.6 0.3	0.8 0.3	0.7 0.3	- -	- -	0.4 0.2
USA: NCS 1990-1992 (Kessler et al., 1994)	8098 (82.6%) general population 15-54 year	CIDI DSM-III-R	Mania	1.6	1.7	1.6	1.4	1.3	1.3	-	-	-
USA: NCS-R 2001-2003 (Merikangas et al., 2007)	9282 (70.9%) general population > 17 year	WMH-CIDI DSM-IV	Bipolar I disorder Bipolar II disorder Subthreshold bipolar disorder	0.8 0.9 2.6	1.1 1.3 2.1	1.0 1.1 2.4	- - -	- - -	0.6 0.8 1.4	- - -	- - -	- - -
USA, Alaska, Hawaii 2001-2002 (Grant et al., 2005)	43093 (81%) general population >17 year	AUDADIS DSM-IV	Bipolar I disorder	3.2	3.4	3.3	1.8	2.2	2.0	-	-	-
Canada 1983-1986 (Fogarty et al., 1994)	3259 (71.6%) general population Edmonton >18 year	DIS DSM-III	Mania	0.7	0.4	0.6	-	-	0.2	-	-	0.1
Canada: CCHS 2002 (Schaffer et al., 2006)	36984 (77%) general population > 15 year	CCHS 1.2 interview DSM-IV	Mania	2.2	2.1	2.2	-	-	-	-	-	-

Study	Population (response)	Instrument Classification	Diagnosis	Lifetime			12-month			1-month		
				M	F	total	M	F	total	M	F	total
Germany: EDSP 1995 (Wittchen et al., 1998)	3021 (71%) general population Munich 14-24 year	M-CIDI DSM-IV	Bipolar I disorder	1.1	1.7	1.4	0.9	1.6	1.3	-	-	-
			Bipolar II disorder	0.2	0.7	0.4	0.1	0.7	0.4	-	-	-
			Single episode mania	0.0	0.1	0.1	0.1	0.1	0.1	-	-	-
			Hypomania	1.4	1.7	1.5	0.9	1.5	1.2	-	-	-
Germany 1998-1999 (Jacobi et al., 2004)	7124 (61.4%) general population 18-79 year	M-CIDI DSM-IV	Any bipolar disorder	0.8	1.2	1.0	0.6	1.1	0.8	0.3	0.8	0.6
Hungary 1995-1996 (Szadoczky et al., 1998)	2953 (85%) general population 18-64 year	DIS DSM-III-R	Bipolar I disorder	1.3	1.6	1.5	-	-	-	-	-	-
			Bipolar II disorder	2.0	2.0	2.0	-	-	-	-	-	-
			Any bipolar disorder	5.7	4.5	5.1	-	-	-	-	-	-
			(Hypo)mania	-	-	-	1.0	0.9	0.9	0.6	0.5	0.5
										point prevalence		
Italy (Faravelli et al., 1990)	1000 (100%) general population Florence > 14 year	Structured interview* DSM-III	Bipolar I disorder	-	-	-	0.65	1.86	1.3	0.22	0.56	0.4
			Bipolar II disorder	-	-	-	-	0.37	0.2	-	0.19	0.1
			Cyclothymia	-	-	-	0.22	0.56	0.4	0.22	0.56	0.4
Italy (Faravelli et al., 2004*a*; 2004*b*; 2006)	2363(94.5%) 609 (99.3%) general population Sesto Fiorentino > 14 year	MINI FPI DSM-IV	Manic/mixed/ hypomanic episode	0.6	0.9	0.8	0.3	0.2	0.3	0.3	0.2	0.3
			Bipolar I disorder	-	-	0.47	-	-	-	-	-	-
			Bipolar II disorder	-	-	0.38	-	-	-	-	-	-
			Subthreshold bipolar disorder	-	-	4.66	-	-	-	-	-	-
The Netherlands: NEMESIS 1996-1999 (Bijl et al., 1998*b*; ten Have et al., 2002)	7076 (64%) general population 18-64 year	CIDI DSM-III-R	Bipolar I disorder	1.37	1.24	1.3	-	-	0.8	-	-	-
			Bipolar disorder NOS	0.24	0.96	0.6	-	-	0.3	-	-	-
			Any bipolar disorder	1.6	2.2	1.9	1.1	1.1	1.1	0.4	0.8	0.6

Study	Population (response)	Instrument Classification	Diagnosis	Lifetime			12-month			1-month		
				M	F	total	M	F	total	M	F	total
Switzerland 1978 1979-1999 (Angst et al., 2003*a*; 2003*b*)	4547 407 (69%) young adults, high risk Zurich 20-41 year	SCL-90-R SPIKE	Bipolar I disorder (DSM-IV)	-	-	0.6	-	-	-	-	-	-
			Bipolar II disorder (DSM-IV)	-	-	1.7	-	-	-	-	-	-
			Bipolar II disorder (Zurich hard criteria)	-	-	5.3	-	-	-	-	-	-
			Bipolar II disorder (Zurich soft criteria)	-	-	5.7	-	-	-	-	-	-
China 2001-2002 (Shen et al., 2006)	5201 (74.7%) general population Shanghai and Beijing 18-70 year	CIDI DSM-IV	Bipolar I-II disorder	-	-	0.1	-	-	-	-	-	-
Japan 1997-1999 (Kawakami et al., 2004)	1029 (56.9%) general population urban community > 19 year	CIDI DSM-III-R	Bipolar I disorder	0.2	-	0.1	-	-	-	-	-	-
Japan 2002-2003 (Kawakami et al., 2005)	1664 (51.6%) general population 2 urban and 2 rural communities > 19 year	WMH-CIDI DSM-IV	Bipolar I - II disorder	-	-	-	-	-	0.1	-	-	-
Taiwan 1982-1986 (Hwu et al., 1989)	5005 metropolitan 3004 small towns 2995 rural villages general population > 18 year	DIS-CM DSM-III	Mania	0.16 0.12 0.12	0.16 0 0.07	0.16 0.07 0.1	- - -	- - -	0.12 0.03 0.1	- - -	- - -	- - -
Brazil: São Paulo ECA study (Moreno et al., 2005)	1464 (76.8%) general population São Paulo > 17 year	CIDI DSM-III-R	Bipolar I disorder	-	-	1.0	-	-	-	-	-	-
			Bipolar II disorder	-	-	0.7	-	-	-	-	-	-
			Subsyndromal hypomania	-	-	2.5	-	-	-	-	-	-
			Manic symptoms	-	-	4.1	-	-	-	-	-	-

Study	Population (response)	Instrument Classification	Diagnosis	Lifetime			12-month			1-month		
				M	F	total	M	F	total	M	F	total
Chile 1992-1999 (Vicente et al., 2004)	2978 (90.3%) general population > 15 year	CIDI DSM-III-R	Mania	-	-	-	-	-	-	0.5	1.3	1.0
Chilli 1999 (Vicente et al., 2005)	75 Indigenous population (Mapuche)	CIDI DMS-III-R	Mania	-	-	1.2	-	-	0	-	-	-
	434 general population > 15 year			-	-	1.5	-	-	1.1	-	-	-
Ethiopia (Negash et al., 2005)	68378 (82.2%) general population rural area, low income country 15-49 year	CIDI/SCAN DSM-III-R	Bipolar I disorder	0.6	0.3	0.5	-	-	-	-	-	-
United Arab Emirates 1996-1997 (Abou-Saleh et al., 2001)	1394 (82%) general population city: AL Ain > 18 year	CIDI ICD 10	Bipolar disorder	0.0	0.7	0.3	-	-	-	-	-	-

***M** = Male; **F** = Female; * structured interview based on the DSM-III criteria for affective disorders and SADS-Lifetime; **AUDADIS** = Alcohol Use Disorder and Associated Disabilities Interview Schedule; **CIDI** = Composite International Diagnostic Interview; **CCHS 1.2** = Canadian Community Health Survey: Mental Health and Well-Being; **CCHS 1.2 interview** = interview based on the WHM-CIDI (trained lay-interviewers), assessed only mania by DSM-IV criteria with a change in duration criterion and number of symptoms: a distinct period of several days and in case of irritable mood 3 additional DSM-IV manic symptoms was enough; **DSM** = Diagnostic and Statistical Manual of Mental Disorders; **DIS** = Diagnostic Interview Schedule; **DIS CM** = Chinese modified Diagnostic Interview Schedule; **ECA** = Epidemiological Catchment Area; **EDSP** = Early Developmental Stages of Psychopathology; **ICD-10** = International Classification of Diseases; **FPI** = Florence Psychiatric Interview: semi-structured interview administered by psychiatrist or advanced trainees in psychiatry interview; **M-CIDI** = Munich Composite International Diagnostic Interview; **MINI** = Mini International Neuropsychiatric International Interview administered by General Practitioner; **NCS** = National Comorbidity Survey; **NCS-R** = National Comorbidity Survey Replication; **NEMESIS** = Netherlands Mental Health Survey and Incidence Study; **SADS-RCD** = Schedule for Affective Disorders and Schizophrenia and the Diagnostic Research Criteria; **SCAN** = Schedules of Clinical Assessment in Neuropsychiatry; **SCL=90-R** = Symptom Checklist 90-R; **SPIKE** = Structured Psychopathological Interview and Rating of Social Consequences for Epidemiology: administered by psychiatric residents and clinical psychologists; **WHM-CIDI** = World Mental Health version of the World Health Organization (WHO) Composite International Diagnostic Interview*

The Hungarian community study determined a lifetime prevalence of any bipolar disorder of 5.1% with the DIS/DSM-III-R (Szadoczky et al., 1998). Respondents with bipolar I or II disorder, only hypomania, and atypical bipolar disorder were included.

Re-analysis of the US National ECA database showed a lifetime prevalence of subthreshold bipolar disorder of 5.1% when respondents were included who experienced two or more lifetime manic symptoms lasting at least one week without meeting the full criteria for a (hypo)manic episode (Judd & Akiskal, 2003).

A Brazilian survey found lifetime prevalence for subsyndromal hypomania, defined as the presence of two or more manic symptoms plus euphoria or irritability for at least two days, with clinical significance of 2.5% and without clinical significance of 4.1% (Moreno & Andrade, 2005).

The Sesto Fiorentino Study found a prevalence of DSM-IV subthreshold bipolar disorder of 4.66%, including respondents with 1) euphoria or irritability but less than three other manic symptoms, 2) no euphoria or irritability but three or more other manic symptoms, and 3) hypomania but no lifetime depressive episode (Faravelli et al., 2006). A required duration of symptoms was not set.

In the NCS-R, respondents were classified as having subthreshold bipolar disorder if they met the following criteria: 1) recurrent subthreshold hypomania (at least two criterion B symptoms such as grandiosity or decreased need to sleep along with all the other criteria for DSM-IV hypomania) in the presence of a major depressive episode, 2) recurrent hypomania in the absence of a major depressive episode, and 3) recurrent subthreshold hypomania in the absence of a major depressive episode. A prevalence for subthreshold bipolar disorder of 2.4% was found (Merikangas et al., 2007). As illustrated by the above-mentioned studies, the prevalence of bipolar spectrum disorder varied between 4.4% and 11 %, depending on the criteria used.

Outline of the thesis

In the present studies of this thesis we investigated the prevalence of various bipolar spectrum disorders and its consequences, i.e. societal costs and quality of life, of suffering from bipolar spectrum disorder in the general population. Transition rates from subthreshold depression and subthreshold (hypo)mania to a clinical syndrome were studied and the independent influence of manic and depressive symptoms on help-seeking behaviour was determined. We also investigated the degree of recognition and treatment of bipolar spectrum disorder in the general population and examined factors that influence detection and receiving adequate treatment.

In the Netherlands Mental Health Survey and Incidence Study (NEMESIS), a fully structured interview (Composite International Diagnostic Interview, CIDI, Robins et al., 1988) was used (Bijl et al., 1998*a*). An ongoing debate is how diagnoses based on structured interviews administered by lay interviewers compares with diagnoses based on semi-structured interviews performed by clinicians, such as the Structured Clinical interview for DSM (SCID, Spitzer et al., 1992). Although it has been claimed that the CIDI is a reliable instrument in general and also to diagnose bipolar I disorder (Wittchen, 1994), its validity towards clinical diagnosis is uncertain. The CIDI probably results in an overestimation of at least some diagnoses. In a small follow-up study of the NCS, 31 respondents with a CIDI/DSM-III-R diagnosis bipolar I disorder were re-interviewed with the SCID. Only 10 of these respondents (28%) fulfilled the criteria for a SCID/DSM-III-R diagnosis bipolar I disorder (Kessler et al., 1997). This study does not provide data on the respondents with a CIDI diagnosis bipolar disorder NOS.

Therefore, we performed a reappraisal study among all NEMESIS respondents with any CIDI/DSM-III-R bipolar disorder (bipolar I disorder and bipolar disorder NOS) to compare these diagnoses with clinical diagnoses based on the SCID/DSM-IV and to estimate the prevalence of bipolar spectrum disorder based on the SCID among respondents with a CIDI diagnosis bipolar disorder. We investigated the possible explanations for discrepancies between diagnoses based on the CIDI/DSM-III-R versus the SCID/DSM-IV. In addition, we examined whether a possible overdiagnosis would be explained by the presence of cluster B personality disorders based on the presumed overlap between bipolar disorder and personality disorder (Akiskal, 2002). (Chapter 2)

Few studies have been published on the self-reported quality of life of people with bipolar disorder (Vojta et al., 2001, ten Have et al., 2002). In addition, the impact of bipolar disorder on social and occupational functioning in the Netherlands is unknown. To study these questions, we determined the societal costs (direct costs generated by use of medical resources as well as indirect costs generated by productivity losses due to absence of work and reduced efficiency at work) and the quality of life of the respondents with a lifetime SCID/DSM-IV bipolar spectrum disorder in the reappraisal study (Chapter 3).

Not only do bipolar I and II disorder reduce the quality of life and cause impairment in functioning, but also subthreshold depression and subthreshold (hypo)mania, defined as a distinct period of depressive or (hypo)manic symptoms without fulfilling the DSM-III-R/IV criteria for a mood disorder, are relevant in terms of health service use, quality of life and impairment (Angst & Merikangas, 1997; Judd et al., 2002; Angst et al., 2003a; Cuijpers & Smit 2004; Cuijpers et al., 2004). Prevalences up to 13% and 8.9% have been reported for subthreshold depression and subthreshold (hypo)mania,

respectively (Angst & Merikangas, 1997; Angst et al., 2003a). This supports the idea that mood disorders are distributed in populations as continua, of which only some come in contact with mental health services.

Given the likely existence of a continuous distribution of mood symptoms with graded impact on functioning and well-being, the study of transition from one position on the continuum to the other becomes relevant. Prospective studies of subthreshold depression have shown an increased risk of future major depressive disorders (Angst & Merikangas, 1997; Cuijpers & Smit, 2004; Cuijpers et al., 2004). For bipolar disorder, the only known prospective data are those of the Oregon Adolescent Depression Project (Lewinsohn et al., 2000; Lewinsohn et al., 2003), which suggest a predictive value of manic symptoms for developing major depressive disorders, anxiety disorders and suicidal behaviour but not for bipolar disorder. In conclusion, relatively little is known about the prognosis of subthreshold mood disorder in terms of transition to a DSM-III-R/IV disorder. Therefore, we investigated in the NEMESIS population the relationship between the subthreshold and clinical expression of mood disorders over time (Chapter 4).

Berkson (1946) stated that the high rates of comorbidity seen in clinical settings may in part be an artefact if the separate comorbid disorders independently influence help-seeking behaviour and need for care. Since the original concept of bipolar disorder is essentially based on observations of help-seeking individuals who have come to the attention of clinicians, the observed association between depressive and manic episodes in clinical practice may be influenced by treatment-seeking. If a treatment-seeking bias (so-called Berkson's bias) accounts in part for a high correlation between manic and depressive symptoms in patient populations, correlations should be much lower in the general population than in clinical populations. We tested this hypothesis in the NEMESIS population. We examined whether manic and depressive dimensions independently contributed to the mental health service use, and determined the degree of comorbidity between manic and depressive dimensions in individuals with and without mental health services use (Chapter 5).

Population-based (Regier et al., 1993; Kessler et al., 1997; ten Have et al., 2002; Hirschfeld et al., 2003*a*; Wang et al., 2005; Schaffer et al., 2006*b*) and clinical studies (Manning et al., 1997; Hantouche et al., 1998; Ghaemi et al., 1999; Ghaemi et al., 2000; Das et al., 2005; Hirschfeld et al., 2005; Mantere et al., 2005) showed that bipolar disorder is underdiagnosed and undertreated. Retrospective studies among patients with bipolar disorder reported long delays between the onset of the first symptoms or the first (hypo)manic episode and receiving the correct diagnosis and treatment (Lish et al., 1994; Suppes et al., 2001; Hirschfeld et al., 2003*b*; Morselli et al., 2003).

Also in NEMESIS indications for high rates of underdiagnosis (54%) and undertreatment (85%) among the respondents with a CIDI/DMS-III-R diagnosis bipolar disorder were found (ten Have et al., 2002). Respondents who did not have contact with mental health care suffered more often from bipolar disorder NOS and had less comorbid disorders (ten Have et al., 2002).

It should be noted that epidemiological studies in the general population ask only globally about diagnostic and treatment issues. Whether the respondent ever had contact with a medical doctor or mental health specialist (Wittchen et al., 2004) or whether they mentioned (hypo)manic symptoms to a medical doctor or mental health care professional counts as an indicator of recognition of the (hypo)manic episode (ten Have et al., 2002). Yet, it remains unclear which factors can explain underrecognition and undertreatment. Therefore, we determined the degree of recognition and treatment among the respondents in the reappraisal study with a SCID/DSM-IV bipolar spectrum disorder and investigated factors that might explain underdetection and undertreatment (Chapter 6).

Finally in chapter 7 we summarize and discuss the findings and their implications for clinical practice and further research.

Methods

Netherlands Mental Health Survey and Incidence Study (NEMESIS)

The data and respondents for this thesis were taken from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) conducted by the Netherlands Institute of Mental Health and Addiction (Trimbos Institute). The study was carried out at the request of the *Rijksinstituut voor Volksgezondheid en Milieuhygiëne* (RIVM) because only limited information on mental health problems of the Dutch population was available. The only two general population studies in the Netherlands that focused on mental problems were local projects: The Nijmegen Regional Project and the East and Southeast Amsterdam filter study. NEMESIS is the first study on the prevalence of psychiatric morbidity in a representative sample of the Dutch population. In addition, it is the first large-scale nationwide prospective population study with three assessment points (1996,1997 and 1999) over a period of 3 years (Bijl et al., 1998*a*).

Sample

A multistage, stratified, random sampling procedure was first used to select 90 municipalities, then a sample of 15,502 private households. Selected households were sent an introductory letter by the Minister of Health inviting them to participate. Finally

11,140 households were eligible for an interview. Respondents within each household needed to be sufficiently fluent in Dutch and aged between 18-64 years. A total of 7076 respondents provided informed consent and was interviewed at baseline (T0). Depending on the method of calculation the response rate was 64% (of the households eligible for interviewing) or 69.7% (of the adults eligible for interviewing). At the second assessment point (T_1), 5618 respondents participated; at the third assessment point (T_2), 4848 respondents participated.

The sample was found to be representative of the Dutch population in terms of gender, marital status and level of urbanisation with the exception of a slight underrepresentation of respondents in the age group 18-24 years (Bijl et al., 1998*a*). Examination of attrition suggested that, after adjustment for influences of demographic variables, this had occurred largely independent of the variable of interest: mental health (de Graaf et al., 2000).

NEMESIS was conducted with the approval of the Internal Review Board of the Trimbos Institute, and after oral explanation of the study in addition to the introductory letter, all respondents gave informed consent to participate in the study as required by Dutch law at the time of the investigation. Respondents were interviewed at home.

Diagnostic instrument

The Composite International Diagnostic Interview (CIDI) version 1.1 (Robins et al., 1988; World Health Organization, 1990; Smeets & Dingemans, 1993) was used, yielding DSM-III-R diagnoses. The CIDI is a fully structured interview and was designed for trained interviewers who are not clinicians and has been found to have high interrater reliability (Wittchen et al., 1991; Cottler et al., 1991) and high test-retest reliability (Semler et al., 1987; Wacker et al., 1990; Wittchen, 1994). Ninety interviewers experienced in systematic data collection collected the data. They received a 3-day training course in recruiting and interviewing followed by a 4-day course at the WHO-CIDI training centre in Amsterdam. Extensive monitoring and quality checks took place throughout the entire data collection period (Bijl et al., 1998*a*).

Clinically relevant symptoms are analysed by a computer program to reach DSM-III-R diagnoses. According to the DSM-III-R, the CIDI generates two types of bipolar diagnoses: bipolar I disorder and bipolar disorder NOS, which includes bipolar II disorder. Cyclothymia is not a separate diagnosis. The hierarchical rules and exclusion criteria were applied as prescribed by the DSM-III-R.

Mental health service use

NEMESIS recorded the use of professionals and services in the primary care and the mental health care sector. Mental health service use was rated "yes" if respondents reported any lifetime contact with a community mental health centre, a psychiatric outpatient clinic, a private psychiatrist, a psychologist, a psychotherapist, psychiatric admission or day treatment.

Prevalence of psychiatric disorders in the Netherlands: results of the first measurement of NEMESIS

For a better understanding of the studies in this thesis and to place them in context some previous results of NEMESIS are presented. Table 1.5 shows the lifetime, 12-month and 1-month prevalence of DMS-III-R disorders of psychiatric disorders at the first measurement (Bijl et al., 1998*b*). A lifetime prevalence of mood disorders of 19% was found. Major depression, with a lifetime prevalence of 15.4%, was the most common mental disorder and almost 6% of the respondents had a major depression in the year before the interview. Alcohol abuse and simple and social phobia were the next common mental disorders. Nearly 12% of the respondents reported lifetime episodes of alcohol abuse, 10.1% of the respondents suffered from a simple phobia and 7.8% from social phobia. Mood disorders, especially dysthymia, were almost twice as common among women. The lifetime prevalence of dysthymia was overall 6.3%, 8.9% for women, and 3.8% for men. The lifetime and 12-month prevalence of bipolar disorder was 1.8% and 1.1%, respectively. Schizophrenia was uncommon, with a lifetime prevalence of 0.4%, but homeless people and those who stayed for a longer period in a hospital or institution were not included in NEMESIS. It may be assumed that psychotic disorders are common in these groups. Therefore, the prevalence found in NEMESIS for schizophrenia is an absolute minimum (Bijl et al., 1998*a*).

Almost half (45%) of the respondents who had a lifetime psychiatric disorder suffered from more than one disorder (Bijl et al., 1998*b*; Ravelli et al., 1998). The presence of one or more comorbid mental disorder is also common among people suffering from bipolar disorder, especially comorbid substance use disorders (42%-52%) (Fortagy et al., 1994; McElroy et al., 2001) and anxiety disorders (31%-60.7%) (Regier et al., 1990; Fortagy et al., 1994; McElroy et al., 2001). Table 1.6 presents the 12-month prevalence of comorbidity of bipolar disorder with anxiety disorders and substance use disorder. The odds ratios are presented to show the association between bipolar disorder and the comorbid disorder. In order to get a good overview of comorbidity, the exclusion criteria as prescribed by the DSM-III-R were not applied. Therefore, the 12-month prevalence of bipolar disorder differs slightly from the 12-month prevalence presented

in table 1.3 (Ravelli et al., 1998). High odds ratios were found for drug dependence, obsessive compulsive disorder and agoraphobia.

Table 1.5 Prevalence of DSM-III-R disorders in NEMESIS (Bijl et al., 1998b)

	lifetime			12-month			1-month		
DSM-III-R diagnosis	**M**	**F**	**Total**	**M**	**F**	**Total**	**M**	**F**	**Total**
Mood disorders	**13.6**	**24.5**	**19.0**	**5.7**	**9.7**	**7.6**	**2.8**	**5.0**	**3.9**
Major depression	10.9	20.1	15.4	4.1	7.5	5.8	1.9	3.4	2.7
Dysthymia	3.8	8.9	6.3	1.4	3.2	2.3	1.0	2.1	1.6
Bipolar disorder	1.5	2.1	1.8	1.1	1.1	1.1	0.4	0.8	0.6
Anxiety disorders	**13.8**	**25.0**	**19.3**	**8.3**	**16.6**	**12.4**	**6.5**	**12.9**	**9.7**
Panic disorder	1.9	5.7	3.8	1.1	3.4	2.2	0.8	2.2	1.5
Agoraphobia (without panic)	1.9	4.9	3.4	0.9	2.2	1.6	0.6	1.4	1.0
Simple phobia	6.6	13.6	10.1	4.1	10.1	7.1	3.1	8.0	5.5
Social phobia	5.9	9.7	7.8	3.5	6.1	4.8	2.8	4.7	3.7
Generalized anxiety disorder	1.6	2.9	2.3	0.8	1.5	1.2	0.6	1.0	0.8
Obsessive compulsive disorder	0.9	0.8	0.9	0.5	0.4	0.5	0.3	0.2	0.3
Substance use disorder total	**29.7**	**7.4**	**18.7**	**14.1**	**3.5**	**8.9**	**9.2**	**2.4**	**5.8**
Substance abuse disorder	**21.0**	**4.5**	**12.9**	**7.8**	**1.9**	**4.9**	**4.2**	**1.0**	**2.6**
Substance dependence disorder	**10.3**	**3.2**	**6.8**	**6.7**	**1.7**	**4.3**	**5.1**	**1.4**	**3.3**
Alcohol abuse	19.3	3.9	11.7	7.3	1.8	4.6	4.0	0.9	2.5
Alcohol dependence	9.0	1.9	5.5	6.1	1.1	3.7	4.5	0.9	2.7
Drug abuse	2.0	1.1	1.5	0.6	0.3	0.5	0.3	0.2	0.3
Drug dependence	2.1	1.5	1.8	1.0	0.7	0.8	0.9	0.5	0.7
Schizophrenia	**0.4**	**0.3**	**0.4**	**0.2**	**0.2**	**0.2**	**0.1**	**0.2**	**0.2**
Eating disorder	**0.2**	**1.3**	**0.7**	**0.2**	**0.6**	**0.4**	**0.1**	**0.4**	**0.3**
Anorexia nervosa	0.0	2.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0
Bulimia nervosa	0.2	1.1	0.6	0.2	0.6	0.4	0.1	0.4	0.3

Table 1.6 12-month prevalence of comorbidity of bipolar disorder with anxiety disorders and substance use disorder in NEMESIS (Ravelli et al., 1998)

	general population %	bipolar disorder %	odds ratio
Bipolar disorder	1.4	NA	NA
Anxiety disorders			
Panic disorder	2.2	14.4	8.3
Agoraphobia (without panic)	1.6	17.5	15.9
Simple phobia	7.1	31.6	6.4
Social phobia	4.8	38.1	13.8
Generalized anxiety disorder	2.6	27.8	17.5
Obsessive compulsive disorder	0.5	7.2	21.5
Substance use disorder total			
Alcohol abuse	4.6	9.2	2.1
Alcohol dependence	3.7	11.3	3.4
Drug abuse	0.5	N<5	N<5
Drug dependence	0.8	14.4	25.7

NA= not applicable

References

Abou-Saleh MT, Ghubash R, Daradkeh TK. A1 Ain Community Psychiatric Survey. I. Prevalence and socio-demographic correlates. Soc Psychiatry Psychiatr Epidemiol 2001;36:20-8.

Akiskal HS, Walker P, Puzantian VR. King D. Rosenthal TL. Dranon M. Bipolar Outcome in the Course of Depressive Illness; Phenomenologic, Familial, and Pharmacologic Predictors. J of Affect Disord 1983;5:115-128.

Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. Psychiatr Clin North Am 1999;22:517-354.

Akiskal HS. Classification, diagnosis and boundaries of bipolar disorder. In: Maj M, Akiskal HS, Lopez-Ibor JJ, Satorius N (eds.), Bipolar Disorder, Wiley, London, 2002.

Akiskal HS, Akiskal KK, Lancrenon S, Hantouche EG. Fraud J, Gury C, Allilaire J. Validating the bipolar spectrum in the French National EPIDEP Study: Overview of the phenomenology and relative prevalence of its clinical prototypes. J of Affect Disord 2006*a*;96:197-205.

Akiskal HS, Akiskal KK, Lancrenon S, Hantouche E. Validating the soft bipolar spectrum in the French National EPIDEP Study: The prominence of BP-II 1/2. J of Affect Disord 2006*b*;96:207-213.

American Psychiatric Association, Diagnostic and statistical manual of mental disorders, 3rd edition (DSM-III). American Psychiatric Press, Washington, 1980.

American Psychiatric Association, Diagnostic and statistical manual of mental disorders, 3rd edition, revised (DSM-III-R). American Psychiatric Press, Washington, 1987.

American Psychiatric Association, Diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV). American Psychiatric Press, Washington, 1994.

Angst J. Zur Ätiologie und Nosologie endogener depressiver Psychosen. Springer Verlag, Berlin, 1966.

Angst J, Merikangas K. The depressive spectrum: diagnostic classification and course. J Affect Disord 1997;45:31-40.

Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998;50:143-151.

Angst J, Gamma A, Benazzi F, Adjacic V, Eich D, Rössler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 2003*a*;73:133-146.

Angst J. Gamma A. Benazzi F. Ajdacic V. Eich D. Rossler W. Diagnostic issues in bipolar disorder. European Neuropsychopharmacology 2003*b*;13(Suppl. 2):43-50.

Baillarger J. De la folie à double-forme. Ann Med Psychol (Paris) 1854;6:367-391.

Bebbington, P. & R. Ramana. The epidemiology of bipolar affective disorder. Soc Psychiatry Psychiatr Epidemiol 1995;30:279-292.

Berkson J. Limitations of the application of the fourfold table analysis to hospital data. Biometrics 1946;2:47–53.

Boyd JH, Weissman MM. `Epidemiology of affective disorders. A reexamination and future directions. Arch Gen Psychiatry 1981;38:1039-1046.

Bijl RV, van Zessen G, Ravelli A, de Rijk C, Langendoen Y. The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. Soc Psychiatry Psychiatr Epidemiol 1998*a*;33:581-586.

Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 1998*b*;33:587-595.

Breslau J, Aguilar-Gaxiola S, Kendler KS, Su M, Williams D, Kessler RC. Specifying race-ethnic differences in risk for psychiatric disorder in a USA national sample. Psychol Med 2006;36:57-68.

Cottler LB, Robins LN, Grant BF, Blaine J, Towle LH, Wittchen HU, Sartorius N. The CIDI-core substance abuse and dependence questions: cross-cultural and nosological issues. The WHO/ ADAMHA Field Trial. Br J Psychiatry 1991;159:653-658.

Cuijpers P, Smit F. Subthreshold depression as a risk indicator for major depressive disorder: a systemic review of prospective studies. Acta Psychiatr Scand 2004;109:325-331.

Cuijpers P, de Graaf R, van Dorsselaer S. Minor depression: risk profiles, functional disability, health care use and risk of developing major depression. J Affect Disord 2004;79:71-79.

Das AK, Olfson M, Gameroff MJ, Pilowsky DJ, Blanco C, Feder A, Gross R, Neria Y, Lantigua R, Shea S, Weissman MM. Screening for bipolar disorder in a primary care practice JAMA 2005;293:956-963.

Dunner DL, Gershon ES, Goodwin FK. Heritable Factors in the Severity of Affective Illness. Biol Psychiatry 1976:11:31-42.

Dunner DL. A review of the diagnostic status of "bipolar II" for the DSM-IV Work Group on Mood Disorders. Depression 1993:1:2-10.

Egeland JA, Hostetter AM. Amish study, I: affective disorders among Amish, 1976-1980. Am J of Psychiatry 1983;140:56-61.

Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry 1978;35:837-844.

Falret JP. Mémoire sur la folie circulaire. Bulletin de l'Académie de Médecine 1854;19:382-415.

Faravelli C, Guerrini Degl'Innocenti B, Aiazzi L, Incerpi G, Pallanti S. Epidemiology of mood disorders: a community survey in Florence. J Affect Disord 1990;20:135-41.

Faravelli C. Abrardi L. Bartolozzi D. Cecchi C. Cosci F. D'Adamo D. Iacono BL. Ravaldi C. Scarpato MA. Truglia E. Rosi S. The Sesto Fiorentino study: Background, methods and preliminary results lifetime prevalence of psychiatric disorders in an Italian community sample using clinical interviewers. Psychother and Psychosom 2004a;73:216-225.

Faravelli C. Abrardi L. Bartolozzi D. Cecchi C. Cosci F. D'Adamo D. Lo Iacono B. Ravaldi C. Scarpato MA. Truglia E. Prodi PMR. Rosi S. The Sesto Fiorentino study: Point and one-year prevalences of psychiatric disorders in an Italian community sample using clinical interviewers. Psychother and Psychosom 2004b;73:226-234.

Faravelli C, Rosi S, Alessandra Scarpato M, Lampronti L, Amedei SG, Rana N.
Threshold and subthreshold bipolar disorders in the Sesto Fiorentino Study. J Affect Disord 2006;94:111-119.

Fogarty F, Russel JM, Newman SC, Brand RC. Mania. Acta Psychiatr Scand 1994;83 (Suppl. 376):16-23.

Ghaemi SN, Sachs GS, Chiou AM, Pandurangi AK, Goodwin F. Is bipolar disorder still underdiagnosed? are antidepressants overutilized? J Affect Disord 1999;52:135-144.

Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing Bipolar Disorder and the effects of Antidepressants: A Naturalistic Study. J Clin Psychiatry 2000;61:804-808.

Ghaemi SN, Ko JY, Goodwin FK. " Cade's Disease" and Beyond: Misdiagnosis, Antidepressant Use, and a Proposed Definition for Bipolar Spectrum Disorder. W Can J Psychiatry 2002;47:125-134.

Goodwin FK, Jamison KR, Manic-depressive illness. Bipolar Disorder and Recurrent Depression, second edition, Oxford University Press, New York 2007.

Graaf R de, Bijl RV, Smit F, Ravelli A, Vollebergh WA. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Am J Epidemiol 2000;152:1039-1047.

Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, Huang B. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2005;66:1205-15.

Hantouche EG, Akiskal HS, Lancrenon S, Allilaire JF, Sechter D, Azorin JM, Bourgeois M, Fraud JP, Chatenet-Duchene L. Systematic clinical methodology for validating bipolar-II disorder: data in mid-stream from a French national multi-site study (EPIDEP). J Affect Disord 1998;50:163-173.

Have M ten, Vollebergh W, Bijl R, Nolen WA. Bipolar disorder in the general population. Prevalence, consequences and care utilisation: results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). J Affect Disord 2002;68:203-213.

Hirschfeld RM, Calabrese JR, Weissman MM, Reed M, Davies MA, Frye MA, Keck PE, Lewis L, McElroy SL, McNulty JP, Wagner KD. Screening for bipolar disorder in the community. J Clin Psychiatry 2003*a*;64:53-59.

Hirschfeld RM, Lewis LL, Vornik LA. Perceptions of Bipolar Disorder: How Far Have we Really Come? Results of the National Depressive and Manic-Depressive Association 2000 Survey of Individuals with Bipolar Disorder. J Clin Psychiatry 2003*b*;64:161-174.

Hirschfeld RMA, Cass AR, Holt DCL, Carlson CA. Screening for Bipolar disorder in patients treated for depression in a family medicine clinic. Journal Am board Fam Pract 2005;18:233-239.

Hwu H, Yek E, Chang L. Prevalence of psychiatric disorders in Taiwan defined by the Chinese Diagnostic Interview Schedule. Acta Psychiatr Scand 1989;79:136-147.

Jacobi F, Wittchen HU, Holting C, Hofler M, Pfister H, Muller N, Lieb R. Prevalence, co-morbidity and correlates of mental disorders in the general population: results from the German Health Interview and Examination Survey (GHS). Psychol Med 2004;34:597-611.

Jamison KR, An unquiet mind. Alfred A. Knopf, New York 1995. In het Nederland vertaald als: De onrustige geest. Luitingh-Sijthoff, Amsterdam 1996.

Judd LL, Schettler PJ, Akiskal HS. The prevalence, clinical relevance and public health significance of subthreshold depressions. Psychiatr Clin North Am 2002;25:685-689.

Judd, L. L. & Akiskal, S. A. The prevalence and disability of bipolar disorder spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. J Affect Disord 2003;73:123-131.

Kalmbaum KL. Über cyclische irresein. Der Irrenfreund 1882;10:145-157.

Kawakami N, Takeshima T, Ono Y, Uda H, Hata Y, Nakane Y, Nakane H, Iwata N, Furukawa TA,

Kikkawa T. Twelve-month prevalence, severity, and treatment of common mental disorders in communities in Japan: preliminary finding from the World Mental Health Japan Survey 2002-2003. Psychiatry Clin Neurosci 2005;59:441-452.

Kawakami N, Shimizu H, Haratani T, Iwata N, Kitamura T. Lifetime and 6-month prevalence of DSM-III-R psychiatric disorders in an urban community in Japan. Psychiatry Res 2004;121:293-301.

Kessler RC, McGonagle KA, Zhao S. Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric Disorders in the United States. Arch Gen Psychiatry 1994;51:8-19.

Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med 1997;27:1079-1089.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593-602.

Kleist K. Die Gliederung der neuropsychischen Erkrankungen. Monatsschr Psychiatr Neurol 1953;125:526-554.

Klerman GL. The spectrum of mania. Compr Psychiatry 1981;22:11-20.

Kraepelin E. Psychiatrie. Ein Lerhbuch für Studirende und Aertze. II. Band. Sechste Auflage. Verlag Barth, Leipzig, 1899.

Krauthammer C, Klerman GL. Secondary mania: Manic syndromes associated with antecedent physical illness or drugs. Arch Gen Psychiatry 1978:35:1333-1339.

Krauthammer C, Klerman GL. The epidemiology of mania. In: Shopsin B (eds.), Manic Illness. Raven Press, New York, 1979, pp 11-28.

Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. Bipolar Disord 2000;2:281-93.

Lewinsohn PM, Seeley JR, Klein DN. Bipolar disorders in adolescents: epidemiology and suicidal behaviour. In: Geller B, Del Bello M (eds.), Bipolar Disorder in Childhood and Early Adolescence. Guilford Press: New York, 2003, pp 7-24.

Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RMA, The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. J Affect Disord 1994;31:281-294.

Lloyd T, Kennedy N, Fearon P, Kirkbride J, Mallett R, Leff J, Holloway J, Harrison G, Dazzan P, Morgan K, Murray RM, Jones PB; AESOP study team. Incidence of bipolar affective disorder in three UK cities: results from the AESOP study. Br J Psychiatry 2005;186:126-131.

Manning JS, Haykal RF, Connor PD, Akiskal HS. On the nature of depressive and anxious states in a family practice setting: the high prevalence of bipolar II and related disorders in a cohort followed longitudinally. Compr Psychiatry 1997;38:102-108.

Mantere O. the clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS). Bipolar Disord 2004:6:395-405.

McElroy SL, Altshuler LL, Suppes T, Keck PE Jr, Frye MA, Denicoff KD, Nolen WA, Kupka RW, Leverich GS, Rochussen JR, Rush AJ, Post RM. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry 2001;158:420-426.

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. Arch Gen Psychiatry 2007;64:543-552.

Moreno DH, Andrade LH. The lifetime prevalence, health services utilization and risk of suicide of bipolar spectrum subjects, including subthreshold categories in the SAO Paulo ECA study. J Affect Disord 2005;87:231-241.

Morselli PL, Elgie R. GAMIAN-Europe/BEAM survey I: global analysis of a patient questionnaire circulated to 3450 members of 12 European advocacy groups operating in the field of mood disorders. Bipolar Disord 2003;5:265-278.

Negash A, Alem A, Kebede D, Deyessa N, Shibre T, Kullgren G. Prevalence and clinical characteristics of bipolar I disorder in Butajira, Ethiopia: a community-based study. J Affect Disord. 2005;87:193-201.

Os J van, Takei N, Castle DJ, Wessely S, Der G, MacDonald AM, Murray RM. The incidence of mania: time trends in relation to gender and ethnicity. Soc Psychiatry Psychiatr Epidemiol 1996;31:129-136.

Os J van, Gilvarry C, Bale R, van Horn E, Tattan T, White I, Murray R. A comparison of the utility of dimensional and categorical representations of psychosis. Psychol Med 1999;29:595-606.

Perris C. A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses: I: Genetic investigation. Acta Psychiatr Scand 1966;42 (Suppl. 194):15-44.

Ravelli A, Bijl RV, van Zessen G. Comorbiditeit van psychiatrische stoornissen in de Nederlandse bevolking; resultaten van de Netherlands Mental health Survey and Incidence Study (NEMESIS). Tijdschrift voor Psychiatrie 1998;40:531-544.

Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990;264:2511-2518.

Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK. The de facto US mental and addictive disorders service system. Epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry 1993;50:85-94.

Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, Farmer A, Jablenski A, Pickens R, Regier DA, et al.. The composite international diagnostic interview: an epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 1988;45:1069-1077.

Schaffer A, Cairney J, Cheung A, Veldhuizen S, Levitt A. Community survey of bipolar disorder in Canada: lifetime prevalence and illness characteristics. Can J Psychiatry 2006*a*;51:9-16.

Schaffer A, Cairney J, Cheung AH, Veldhuizen S, Levitt A. Use of Treatment Services and Pharmacotherapy for Bipolar Disorder in a general Population-Based Mental health Survey. J Clin Psychiatry 2006*b*;67:386-393.

Semler G, Wittchen HU, Joschke K, Zaudig M, von Geiso T, Kaiser S, von Cranach M, Pfister H. Test-retest reliability of a standardized psychiatric interview (DIS/CIDI). Eur Arch Psychiatry Neurol Sci 1987;236:214-222.

Shen YC, Zhang MY, Huang YQ, He YL, Liu ZR, Cheng H, Tsang A, Lee S, Kessler RC. Twelve-month prevalence, severity, and unmet need for treatment of mental disorders in metropolitan China. Psychol Med 2006;36:257-267.

Smeets RMW, Dingemans PMA J. Composite International Diagnostic Interview (CIDI) Version 1.1. World Health Organization, Amsterdam Geneva, 1993.

Spitzer, R.L., J. Endicott & E. Robins, Research diagnostic criteria (RDC) for a selected group of functional disorders, 3rd edition. New York State Psychiatric Institute, New York, 1978.

Spitzer RL, Williams JBW, Gibbon M, First MB. The structured clinical interview for DSM-II-R (SCID). I: history, rationale and description. Arch Gen Psychiatry 1992;49:624-629.

Suppes T, Leverich GS, Keck PE, Nolen WA, Denicoff KD, Altshuler LL, McElroy SL, Rush AJ, Kupka R, Frye MA, Bickel M, Post RM. The Stanley Foundation Bipolar Treatment Outcome Network. II. Demographics and illness characteristics of the first 261 patients. J Affect Disord 2001;67:45-59.

Szadoczky E, Papp Z, Vitrai J, Rihmer Z, Furedi J. The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. J Affect Disord 1998;50:153-162.

Vicente B, Kohn R, Rioseco P, Saldivia S, Baker C, Torres S. Population prevalence of psychiatric disorders in Chile: 6-month and 1-month Rates. Br J Psychiatry 2004;184:299-305.

Vicente B, Kohn R, Rioseco P, Saldivia S, Torres S. Psychiatric disorders among the Mapuche in Chile. Int J Soc Psychiatry 2005;51:119-127.

Vojta C, Kinosian B, Glick H, Altshuler L, Bauer MS. Self-reported quality of life across mood states in bipolar disorder. Compr Psychiatry 2001;42:190-195.

Wacker HR, Battegay R, Mullejans R, Schlosser C. Using the CIDI in the general population. In: Stefanis CN, Rabavilas AD, Soldatos CR (eds.), Psychiatry: a world perspective, Elsevier Science Publishers, Amsterdam, 1990, pp.138-143.

Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:629-640.

Weissman MM, Myers JK. Affective disorders in a US urban community: the use of research diagnostic criteria in an epidemiological survey. Arch Gen Psychiatry 1978;35:1304-1311.

Weissman MM, Leaf PJ, Tischler GJ, Blazer DG, Karno M, Bruce ML, Florio LP. Affective disorders in five United States communities. Psychol Med 1988;18:141-153.

Weissman MM, Bruce ML, Leaf PJ, Florio LP, Holzer C. Affective disorders. In: Robins LN, Regier DA (eds.), Psychiatric disorders in America, Free Press, New York, 1991, pp. 55-81.

Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. Br J Psychiatry 1991;159:645-653.

Wittchen H. Reliability and validity studies of the WHO-composite international diagnostic interview (CIDI): a critical review. J Psychiatr Res 1994;28:57-84.

Wittchen HU, Nelson CB, Lachner G. Prevalence of mental disorders and psychosocial impairments in adolescents and young adults. Psychol Med 1998;28:109-126.

World Health Organization, Composite International Diagnostic Interview (CIDI). WHO, Geneva, 1990.

World Health Organization, The ICD-10 classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines. WHO, Geneva, 1992.

CHAPTER 2

PREVALENCE OF BIPOLAR DISORDER IN THE GENERAL POPULATION; A REAPPRAISAL STUDY OF THE NETHERLANDS MENTAL HEALTH SURVEY AND INCIDENCE STUDY (NEMESIS)

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Abstract

Objective

NEMESIS is a Dutch population study using a fully structured interview (CIDI), administered by trained interviewers. Based on all three assessments of NEMESIS, 2.4% of the respondents were identified with lifetime bipolar disorder (DSM-III-R).
The primary aim of the study was to estimate the prevalence of bipolar disorder in the same population based on a semi-structured interview administered by clinicians.

Method

Seventy-four persons identified with a lifetime CIDI/DSM-III-R bipolar disorder and 40 persons with a major depressive disorder (MDD) were re-interviewed with the SCID.

Results

Based on the SCID, 30/74 respondents with a CIDI/DSM-III-R bipolar disorder and 8/40 respondents with MDD met DSM-IV criteria for bipolar disorder or cyclothymia, corresponding with an adjusted lifetime prevalence in these groups of 1 % (95% CI 0.7-1.3%) and 4.2% (95% CI 1.6%-6.9%), respectively.

Conclusion

Compared to the SCID the CIDI on the one hand overdiagnoses bipolar disorder but on the other hand underdiagnoses bipolar disorder.

Key words: bipolar disorder, diagnosis, prevalence

Introduction

Although bipolar disorder exists all over the world, the lifetime prevalence varies largely between studies: for bipolar I disorder (with manic episodes) between 0.2 and 1.6% and for the whole bipolar spectrum, in which bipolar II disorder (with only hypomanic episodes and major depressive episodes) and cyclothymia (hypomanias and minor depressions) are also included, between 3 and 7% (Angst & Marneros 2001). These different prevalence rates may be explained partly by different diagnostic instruments and different classification systems used in the various studies, as well as by different study populations.

Three general population studies have used fully structured interviews administered by trained lay interviewers, such as the Diagnostic Interview Schedule (DIS, Robins et al., 1981) and the Composite International Diagnostic Interview (CIDI, WHO, 1990) to asses the prevalence of mental disorders according to the criteria of DSM-III or DSM-III-R, respectively. In these studies a lifetime prevalence of bipolar I disorder was found ranging from 0.8% in the US Epidemiological Catchment Area (ECA) study (Robins et al., 1991) based on the DIS/DSM-III, to 1.6% in the US National Comorbidity Survey (NCS) (Kessler et al., 1994) and 1.3% in the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (ten Have et al., 2002) both based on the CIDI/DSM-III-R. In addition, lifetime prevalence for total bipolar disorder, i.e. bipolar I disorder and bipolar disorder not otherwise specified (NOS), in NEMESIS was 1.9%.

An ongoing debate is how diagnoses based on structured interviews administered by lay interviewers compare with diagnoses based on semi-structured interviews performed by clinicians, such as the Structured Clinical Interview for DSM (SCID, Spitzer et al., 1992). Although it has been claimed that the CIDI is a reliable instrument, also to diagnose bipolar I disorder (Wittchen, 1994), its validity towards clinical diagnoses is still uncertain. Probably the CIDI results in an overestimation of at least some diagnoses (Kessler et al., 1997, ten Have et al., 2002).

Regarding bipolar disorder, we are aware of only one general population study in which trained clinicians have applied a semi-structured interview such as the SCID to re-interview respondents with a bipolar disorder diagnosis based on a fully structured interview such as the CIDI. This is a small follow-up study of the NCS by Kessler et al. (1997), in which 31 respondents with a CIDI/DSM-III-R diagnosis of bipolar I disorders were re-interviewed with the SCID. Only 10 of these respondents (28%) also fulfilled the criteria for a SCID/DSM-III-R bipolar I disorder. Unfortunately, this study did not provide data on the respondents with a CIDI/DSM-III-R diagnosis of bipolar disorder NOS. Therefore, we performed a reappraisal study among all NEMESIS respondents diagnosed with any CIDI/DSM-III-R bipolar disorder, i.e. bipolar I and bipolar NOS, to compare these diagnoses with clinical diagnoses based on the SCID/DSM-IV.

Because bipolar II disorder and bipolar disorder NOS were also included it was expected that, instead of the 28% Kessler et al. found, 30-50% would fulfil the criteria of SCID/DSM-IV bipolar disorder. With regard to possible explanations for discrepancies between the diagnoses based on the CIDI/DSM-III-R versus the SCID/DSM-IV, we expected that the more severe cases of bipolar disorder would be diagnosed by both the CIDI and the SCID. Therefore, illness characteristics such as duration of the illness, comorbidity, impairment of psychosocial functioning, number of episodes and number of (hypo)manic symptoms respondents experienced during an episode were examined. In addition we looked for specific symptom profiles, as Kessler et al. had found that the only manic symptom profile that was confirmed by the SCID was characterised by euphoria, grandiosity and the ability to maintain energy without sleep (Kessler et al., 1997). Another explanation could be a difference in minimum duration of the (hypo)manic episode asked for in the CIDI (2 days) versus the SCID (4 days) resulting in diagnosing more respondents with a (hypo)manic episode by the CIDI. Finally, it was hypothesised that a possible overdiagnosis of bipolar disorder by the CIDI would partly be explained by personality disorders, especially of cluster B personality, based on the presumed overlap between bipolar disorder and borderline personality disorder (Akiskal, 2002).

Aims of the study

The first aim of the study was to estimate the prevalence of the bipolar disorder among the respondents with a CIDI diagnosis bipolar disorder in NEMESIS based on a semi-structured interview administered by clinicians. The secondary aim was to investigate the possible explanations for discrepancies between diagnoses based on the CIDI/DSM-III-R versus the SCID/DSM-IV. The third aim of the study was to examine if a possible overdiagnosis of bipolar disorder would be explained by cluster B personality disorders.

Material and methods

Sample

All respondents were derived from NEMESIS, a prospective psychiatric epidemiological survey in the Dutch adult general population (N=7076, aged 18-64) with three assessment points (T_0, T_1 and T_2) in 1996, 1997 and 1999. The participants accurately reflected the Dutch population in terms of gender, civil status and urbanicity. The CIDI was used to determine psychiatric diagnoses according to the criteria of the DSM-III-R. At T_0 the lifetime, one-year and one-month prevalence of psychiatric disorders was established. At T_1 the one-year prevalence and at T_2 the two-year prevalence of

psychiatric disorders were determined. All respondents were kept blind with respect to their diagnosis. Further methods used in NEMESIS are described elsewhere (Bijl et al., 1998).

At T_0 132 (1.9%) respondents fulfilled criteria for bipolar disorder: either bipolar I disorder (N=91, 1.3%) or bipolar disorder NOS (N=41, 0.6%) (6). At T_1 and T_2, 5618 (79,5%) and 4848 (68.5%) of the original sample was interviewed again, resulting in 14 (de Graaf et al., 2002) and 12 new respondents with a bipolar disorder, respectively.

Of all 158 persons (2.4%) who were identified with a lifetime bipolar disorder at any of the three assessment points, 115 had participated in all three interviews, and 105 of them had indicated that they could be contacted in case of follow-up studies. Ultimately 74 (70.5%) of these 105 respondents participated in the current study, i.e. 46.8% of the total sample with a bipolar disorder. The participants (N=74) were significantly older, higher educated and more employed than the non-participants (N=84). There were no significant differences regarding gender, household composition, urbanicity, income and comorbidity and prevalence of bipolar I disorder versus bipolar disorder NOS.

In order to keep the interviewers blind for the original CIDI/DSM-III-R diagnosis, a second group of 57 respondents with a lifetime diagnosis of unipolar major depressive disorder (MDD) was selected. These 57 were randomly selected out of all respondents with MDD (N=1403) from whom 1002 had participated in all three interviews, and 894 had agreed to participate in case of a follow-up study. Finally, 40 (70%) respondents participated in the study. There were no significant differences between the participants and non-participants on sociodemographic factors and comorbidity.

The interviewers - a resident in psychiatry (ER) and a psychologist (MR) - were both intensively trained in the SCID. A senior psychiatrist (WN) was consulted in those cases (N=58, 50.9%) where the interviewers had any doubts how to rate specific symptoms relevant for a diagnosis. The SCID interview was held approximately 2 years after the last CIDI interview in order to avoid possible influence from the three prior interviews, e.g. respondents trying to remember what they had answered in earlier interviews (Kessler et al., 1998). The Medical Ethical Review Board of the UMC Utrecht approved the study and after full explanation of the study, written informed consent was obtained from all participants.

Diagnostic instruments

The CIDI (version 1.1) is a fully structured interview and can be administered by trained interviewers who are not clinicians. Clinically relevant symptoms are analysed by a computer program to reach DSM-III-R diagnoses. In several studies the CIDI showed good test-retest and interrater reliability (Wittchen, 1994), partly due to the fully structured form of the interview with no need of a clinical judgement. According to

the DSM-III-R the CIDI generates two types of bipolar diagnoses: bipolar I disorder and bipolar disorder NOS (which includes bipolar II disorder). Cyclothymia is not a separate diagnosis. The hierarchical rules and exclusion criteria were applied as prescribed by the DSM-III-R.

The SCID for DSM-IV (version 2.0) is a semi-structured interview for diagnosing psychiatric disorders, which has to be administered by trained clinicians. The SCID distinguishes several DSM-IV subcategories of the bipolar disorder: bipolar I disorder, bipolar II disorder, bipolar disorder NOS (including cyclothymia) and as a separate category 'mood disorder induced by substance use, specified with depressive, manic or mixed characteristics'. Tested with the SCID for DSM-III-R in patients with bipolar disorder the test-retest and interrater reliability shows good agreement (Segal et al., 1994; Skre et al., 1991; Williams et al., 1992). The reliability of the SCID is likely to be higher when the focus of the study is on one or two disorders during the SCID interview rather than on all SCID diagnoses (Williams et al., 1992).

Prevalence of bipolar disorder

In order to calculate the prevalence of bipolar disorder, we first multiplied the percentage of respondents with a SCID/DSM-IV bipolar disorder among the CIDI/DSM-III-R bipolar disorder group with the total 2.4% prevalence of bipolar disorder based on all three assessments of NEMESIS. The 95% confidence interval is calculated with the standard error of the proportion of the respondents. Next, we followed the same procedure for the CIDI/DSM-III-R MDD group, taken into account a total lifetime prevalence of CIDI/DSM-III-R MDD based on all three assessments of 21.2%. Finally, we added the two obtained prevalence rates.

Possible explanations for discrepancies between CIDI and SCID diagnoses

The following potential explanations were studied: Sociodemographic factors (gender and age) and illness characteristics (mean duration of the illness, number of depressive and (hypo)manic episodes, number of symptoms ever experienced during a (hypo)manic episode, comorbid SCID/DSM-IV diagnoses, comparison of single symptoms and impairment of psychosocial functioning).

To diagnose a (hypo)manic episode according to either CIDI or SCID, a respondent had to report a distinct period of abnormally and persistently elevated, expansive or irritable mood. Furthermore at least 3 (or 4 if the mood is irritable) of the following symptoms had to be present: inflated self-esteem or grandiosity, decreased need for sleep, more talkative or pressured speech, flight of ideas or subjective experience that thoughts are racing, distractibility (attention is easily drawn to unimportant or irrelevant external stimuli), increase in goal-directed activity (either socially, at work or school, or sexually), psychomotor agitation (inability to sit still), involvement in

pleasurable activities which have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments). There are however differences between CIDI and SCID. In the CIDI, the minimum duration of an episode with euphoric or irritable mood is 2 days. However, it does ask for the number of days the longest (hypo)manic episode had lasted. In the SCID, the duration of the episode with changed mood must have been at least 4 days for a hypomanic episode or 7 days for a manic episode. To assess the impairment of psychosocial functioning we applied the MOS Short-Form Health Survey (SF-36), an instrument containing 36 items grouped into eight scales: general health perceptions, physical functioning, role limitations due to physical problems, pain, vitality, social functioning, mental health and role limitations due to emotional problems (Ware & Sherbourne, 1992). We used the last three scales to measure psychosocial functioning.

Finally, we also applied the Personality Disorders Questionnaire for DSM-IV (PDQ-4+, Hyler, 1994). The PDQ is an easily administered, self-report questionnaire to assess personality disorders, with high sensitivity but moderate specificity (Hyler et al., 1990).

Statistics

The analyses reported below were carried out with SPSS 8.0 for Windows. We used summary statistics (percentages, means) to describe the sample. To compare the diagnoses based on the CIDI with the diagnoses based on the SCID and to determine the percentage of respondents with CIDI and SCID diagnosis bipolar disorders, we used cross-tabulations. The data-analysis of the possible explanations for discrepancies between the diagnoses based on the CIDI versus the SCID was carried out with cross-tabulations, one-way Anova procedures and Chi Square test of significance.

Results

Comparison of CIDI and SCID diagnoses

As shown in table 2.1, 30 (40.5%) of all 74 respondents with a CIDI/DSM-III-R bipolar disorder, met criteria for a SCID/DSM-IV bipolar disorder. Of the 49 respondents with a CIDI bipolar I disorder, 19 (38.8%) were diagnosed with any bipolar disorder by the SCID, including 11 (22.4%) with a SCID bipolar I disorder. Of the 25 respondents with a CIDI bipolar disorder NOS 11 (44%) had a SCID diagnosis of bipolar disorder (differences not significant).

Table 2.1 also lists the primary lifetime SCID/DSM-IV disorders of the 44 respondents who were not diagnosed by the SCID with a bipolar disorder. The majority (70.5%) of these respondents met the criteria for any lifetime depressive disorder.

Table 2.2 lists the SCID/DSM-IV diagnoses among the 40 respondents of the group with a CIDI/DSM-III-R diagnosis MDD. Eight of them (20%) fulfilled the criteria for a DSM-IV bipolar disorder, plus another two respondents (5%) who had developed their first hypomanic episode in the two years between the last CIDI interview of the NEMESIS (T2) and the SCID interview.

Table 2.1 Primary lifetime disorders according to SCID/DSM-IV in 74 respondents with CIDI/DSM-III-R diagnoses of bipolar disorder

	CIDI/DSM-III-R diagnosis		
SCID/DSM-IV diagnosis	**Bipolar I disorder (N=49)**	**Bipolar disorder NOS (N=25)**	**Bipolar disorders total (N=74)**
Bipolar disorders total	**19#**	**11**	**30#**
Bipolar I disorder	11	0	11
Bipolar II disorder	5#	6	11#
Bipolar disorder NOS	1	4	5
Cyclothymia	1	1	2
Bipolar disorder, substance (antidepressant) induced	1	0	1
Depressive disorders total	**20**	**11**	**31**
Major depressive disorder	19	8	27
Dysthymic disorder	0	1	1
Depressive disorder NOS	1	2	3
Other diagnoses total	**5**	**1**	**6**
Schizophrenia (primary diagnosis)	1	0	1
Psychotic disorder NOS (primary diagnosis)	1	1	2
Substance use disorder (primary diagnosis)	3	0	3
No diagnosis	**5**	**2**	**7**

 # indicates a respondent who developed a manic episode during the use of an antidepressant

NOS = Not otherwise specified

Table 2.2 Primary lifetime disorders according to SCID/DSM-IV in 40 respondents with a CIDI/DSM-III-R diagnosis of major depressive disorder

	CIDI/DSM-III-R diagnosis
SCID/DSM-IV diagnosis	**Major depressive disorder (N=40)**
Bipolar disorders total	**10$$**
Bipolar I disorder	3
Bipolar II disorder	3$
Bipolar disorder NOS	2$
Cyclothymia	1
Bipolar disorder, substance (antidepressant) induced	1
Depressive disorders total	**23**
Major depressive disorder	20
Dysthymic disorder	1
Depressive disorder NOS	2
Other diagnoses total	**2**
No diagnosis	**5**

$ indicates a respondent who developed the first hypomanic episode after the last CIDI interview
NOS = Not otherwise specified

Lifetime prevalence of bipolar disorder

With the finding that 40.5% (*P*=0.405, SEp= 0.0575 CI: 0.29-0.53) of the respondents with a CIDI/DSM-III-R bipolar disorder also fulfilled the criteria for a SCID/DSM-IV bipolar spectrum disorder, the adjusted prevalence of DSM-IV bipolar spectrum disorders based on the respondents with a CIDI/DSM-III-R bipolar disorder is 1.0% (95% CI: 0.7% - 1.3%) The adjusted prevalence is calculated by taken 40.5 % of the total 2.4 % lifetime prevalence bipolar disorder based on all three assessments of NEMESIS. Eleven of all 30 (36.7%) respondents with a SCID/DSM-IV bipolar disorder fulfilled the criteria for a bipolar I disorder. Therefore the adjusted lifetime prevalence of bipolar I disorder is 0.4% (95% CI: 0.2% - 0.6%) (table 2.3).

Because 2 of the 10 respondents developed their first (hypo)manic episode after the last NEMESIS interview these respondents were not included in the calculation of the prevalence based on the respondents with a CIDI/DSM-III-R MDD. The total lifetime prevalence of CIDI/DSM-III-R MDD based on three assessments was 21.2%. With the finding that 20% (*P*=0.2, SEp=0.064 CI: 0.074-0.326) of these respondents had a SCID/DSM-IV bipolar disorder, the adjusted prevalence of DSM-IV bipolar spectrum

disorder in this group is 4.2% (95% CI: 1.6%-6.9%).

When we add these two prevalence rates the total lifetime prevalence of SCID/DSM-IV bipolar spectrum disorders, based on the groups with any CIDI/DSM-III-R major mood disorder (bipolar disorder or MDD), is 5.2% (95% CI: 2.2-8.1)

Table 2.3 Lifetime prevalence in the general population of the subtypes of bipolar disorder according to SCID/DSM-IV

	Based on respondents with CIDI/DSM-III-R bipolar disorder	Based on respondents with CIDI/DSM-III-R major depressive disorder	Based on respondents with CIDI/DSM-III-R major mood disorder
Bipolar spectrum disorder total	**1.0 (95% CI: 0.7-1.3)**	**4.2 (95% CI: 1.6-6.9)**	**5.2 (95% CI: 2.2-8.1)**
Bipolar I disorder	0.4 (95% CI: 0.2-0.6)	1.6 (95% CI: -0.1-3.6)	2.0 (95% CI: 0.1-4.1)
Bipolar II disorder	0.4 (95% CI: 0.2-0.6)	1.1 (95% CI: -0.4-2.5)	1.5 (95% CI: -0.2-3.1)
Bipolar disorder NOS	0.2 (95% CI: 0.02-0.3)	0.5 (95% CI: -0.5-1.6)	0.7 (95% CI: -0.5-1.9)
Cyclothymia	0.1 (95% CI: -0.02-0.2)	0.5 (95% CI: -0.5-1.6)	0.6 (95% CI: -0.5-1.7)
Bipolar disorder, substance (antidepressant) induced	0.03 (95% CI: -0.03-0.1)	0.5 (95% CI: -0.5-1.6)	0.53 (95% CI: -0.5-1.7)

NOS = Not otherwise specified, CI = Confidence interval

Possible explanations for discrepancies between the CIDI and SCID diagnoses

The comparison of the respondents with both a CIDI/DSM-III-R bipolar disorder and a SCID/DSM-IV bipolar disorder (CIDI BD/SCID BD) (N=30) with the respondents with a CIDI/DSM-III-R bipolar disorder but no SCID/DSM-IV bipolar disorder (CIDI BD/SCID non-BD) (N=44) on sociodemographic factors and illness characteristics is presented in table 2.4.

There were no significant differences between the groups regarding gender or age. Age of onset was younger in the CIDI BD/SCID BD group than in the CIDI BD/SCID non-BD group, but not significant. As a result the mean duration of illness is larger in the CIDI BD/SCID BD group, but again not significant.

The number of previous depressive or (hypo)manic episodes based on the CIDI did not differ between the groups. In both groups most respondents reported 1-3 depressive as well as 1-3 (hypo)manic episodes during their life. Based on the CIDI the number of symptoms respondents ever experienced during a (hypo)manic episode was not different between groups. However, based on the SCID the mean -number of (hypo)manic symptoms was significantly less in the group CIDI BD/SCID non-BD, explaining the different SCID/DSM-IV diagnoses.

Based on CIDI interviews 80% of the respondents in the CIDI BD/SCID BD group indicated that their longest (hypo)manic episode had lasted 4 days or more. In the CIDI BD/SCID non-BD group 86.4% of the respondents reported a (hypo)manic episode of 4 days or more.

Table 2.4 Sociodemographic and illness characteristics of respondents with CIDI BD/SCID BD compared with respondents with CIDI BD/SCID non-BD

	CIDI BD / SCID BD (N=30)	**CIDI BD / SCID non-BD (N=44)**
Mean age (median)	42.9 (40.4)	44.2 (43.2)
Female (%)	56.7	56.8
Mean age of onset any symptoms (median)	24.8 (24.5)	30 (27.5)
Mean duration of illness (median)	18.6 (16.3)	15.8 (14.6)
Number of episodes based on the CIDI (%)		
• (Hypo)manic episodes		
1-3	36.7	40.9
4-10	10	13.6
>10	36.7	34.1
Unknown	16.7	11.4
• Depressive episodes		
1-3	50	38.6
4-10	13.3	18.2
>10	23.3	20.5
Unknown	13.3	22.7
Mean number of symptoms ever experienced in a (hypo)manic episode:		
◊ Based on the CIDI (median)	6.5 (6)	6.2 (6)
◊ Based on the SCID (median)	6.6 (7)	1.4 (1)
Duration of most severe (hypo)manic episode		
◊ ≥ 4 days based on the CIDI (%)	80	86.4
◊ ≥ 4 days based on the SCID (%)	100	not applicable
Mean number of comorbid SCID diagnoses per respondent (median)	0.9 (1)	0.6 (1)
Respondents with:		
• Substance use disorder (%)	20	22.7
• Anxiety disorder (%)	36.7	36.4
• Eating disorder (%)	10	9.1
• Other	6.7	0
Psychosocial functioning based on the mean scores of the MOS SF-36 (rang from 0 to 100 with higher scores indicating better functioning) on the following scales:		
• Social functioning	78.3	80.4
• Mental health	71.6	69.3
• Emotional role limitations	66.7	69.8

No differences were found in number of comorbid SCID diagnoses and type of comorbid disorders between the both groups.

Assessed with the MOS SF-36 no significant different scores were found on the social functioning, mental health and emotional role limitations scales between both groups.

Comparison on symptom level

An almost similar symptom pattern, i.e. with no significant differences, was found in both groups. The most reported symptoms with the CIDI in the CIDI BD/SCID BD group were distractibility (90%), inability to sit still (86.7%), racing thoughts (83.3%). Grandiosity was reported by only 13.3% of the respondents. In the CIDI BD/SCID non-BD group the percentages of these symptoms were: distractibility (95.5%), inability to sit still (79.5%) maintaining energy without sleep (81.8%) and grandiosity (4.5%).

Table 2.5 Mean scores and diagnoses according to PDQ-4+ in respondents with CIDI BD/SCID BD and respondents with CIDI BD/SCID non-BD

	CIDI BD / SCID BD (N=30)		**CIDI BD / SCID non-BD (N=44)**	
	Mean score	**Diagnosis %**	**Mean score**	**Diagnosis %**
Cluster A	**5.43**	**20**	**5.20**	**29.5**
Paranoid	1.87	16.7	1.75	20.5
Schizoid	1.67	10.0	1.61	9.1
Schizotypical	1.90	6.7	1.84	11.4
Cluster B	**5.97**	**16.7**	**6.09**	**20.5**
Histrionic	1.80	6.7	2.02	6.8
Narcissistic	1.53	6.7	1.41	4.5
Borderline	2.00	10.0	2.11	13.6
Cluster C	**4.93**	**36.7**	**6.23**	**36.4**
Antisocial	0.63	0	0.55	2.3
Avoidant	1.77	23.3	2.36	27.3
Dependent	0.70	0	1.34	9.1
Obsessive compulsive	2.47	26.7	2.52	27.3
Negativistic	1.10	3.3	1.20	4.5
Total	**19.53**	**56.7**	**21.69**	**50**

Personality disorders

The outcome of the PDQ-4+ in both groups is shown in table 2.5. The majority of the personality disorders found were in the categories of paranoid, avoidant and obsessive-compulsive personality disorders. Both mean scores per personality disorder and number of diagnoses (in percentages) made by the PDQ-4+, did not differ significantly between the groups. Also if we look at differences between the two groups divided in cluster A, B and C personality disorders, no significant differences were found.

Discussion

We found that bipolar disorder is both overdiagnosed and underdiagnosed by the CIDI when compared to the SCID. As we expected, less than half (40.5%) of the respondents with a DSM-III-R bipolar disorder based on the CIDI also fulfilled DSM-IV criteria for bipolar disorder when interviewed with the SCID. Our finding that among respondents with a CIDI/DSM-III-R bipolar I disorder only 22% also had a SCID/DSM-IV bipolar I disorder, is comparable to the 28%, which was found in the reappraisal study of the NCS (Kessler et al., 1997). In addition and rather unexpectedly we found a prevalence of 20% (8/40 cases) of SCID/DSM-IV bipolar disorder among the respondents with a CIDI/DSM-III-R MDD.

Based on the percentages of SCID/DSM-IV bipolar disorder among respondents with CIDI/DSM-III-R bipolar disorder (1.0%) or MDD (4.2%) we calculated a prevalence of DSM-IV bipolar spectrum disorder based on the group of respondents with a major mood disorder of 5.2% (95% CI 2.2-8.1), including 2% (95% CI 0.1-4.1) for bipolar I disorder. The existence of such a high prevalence supports findings of earlier studies as reviewed by Angst and Marneros (2001). They reported a (lifetime) prevalence of bipolar disorder of 3% to 7%. Recently, Angst et al. (2003) have argued that the current concept of bipolar I and bipolar II disorder may be too narrow. When they used an even broader definition of hypomania ("a syndrome (no minimum duration) characterised by the presence of 1. overactivity, euphoria or irritability; 2. have themselves experienced problems or received comments from others that something must be wrong with them; 3. presence of at least three out of seven signs or symptoms of DSM-IV hypomania"), they found a prevalence rate of bipolar II disorder of 5.3%.

Recently another population survey also found indications for a high prevalence of bipolar disorder (Hirschfeld et al., 2003). In this study over 85,000 subjects, representative for the US population, completed the Mood Disorders Questionnaire (MDQ), which has high specificity but relative low sensitivity for bipolar disorders. The adjusted positive screen rate for bipolar I or bipolar II disorder was 3.7%. Taken together all these data and our data, the impression emerges that bipolar disorder is indeed

more frequent than often thought. This not only counts for bipolar I disorder, but also for the other disorders of the bipolar spectrum, including bipolar II disorders. Failing to diagnose a hypomanic episode in patients with depressive episodes automatically leads to the diagnosis MDD. This is in line with clinical impressions that especially in these patients the diagnosis bipolar II disorder is easily missed (Angst & Gamma, 2002).

Another explanation for the relative high prevalence of bipolar disorder is the design of NEMESIS with three assessment points. Respondents who were diagnosed at least once with a DSM-III-R bipolar disorder or fulfilled the criteria for a lifetime diagnosis. In addition, during the subsequent CIDI interviews a diagnosis of MDD could switch to bipolar disorder, but not vice versa. Therefore, lifetime prevalence of bipolar disorder could only increase over the three assessment points of NEMESIS.

In contrast to the reappraisal study of the NCS (Kessler et al., 1997) we could not find a symptom profile, which predicts the clinical validity of a CIDI diagnosis. Moreover, we did not find clear explanations for the discrepancy between the CIDI/DSM-III-R and SCID/DSM-IV diagnoses. The only difference, although not significant, was an earlier age of onset among the CIDI BD/SCID BD group compared to the CIDI BD/SCID non-BD group. Therefore the overdiagnosis of the bipolar disorder by the CIDI is not explained.

The majority of the personality disorders were found in the categories of paranoid, avoidant and obsessive-compulsive disorders. This does not confirm results of another study among bipolar patients in whom high prevalence's of borderline and histrionic personality disorders were found when assessed with the DSM-III-R version of the PDQ (PDQ-R) (O'Connell et al., 1991). However, differences may be explained be the fact that their study implied a clinical population and our sample was from the general population.

Our study has several limitations. First, we could not perform a SCID interview in all NEMESIS respondents with a lifetime CIDI/DSM-III-R bipolar disorder, but in only 46.8% of them (74/158). Between the first CIDI interview and this fourth interview with the SCID 53.2% (84/158) of all respondents with a lifetime CIDI bipolar disorder had dropped out. The participants were significantly older, higher educated and more employed than the non-participants. Nevertheless we assume that our sample was relatively representative for the whole NEMESIS population. This assumption is supported by earlier findings in the NEMESIS that the most common reason for drop out was failure to locate the respondent, while psychopathology had only moderate effects on attrition and was mainly related to failure to locate and morbidity/mortality but not to refusal (de Graaf et al., 2000).

Second, the number of respondents in both groups was rather small, especially the group with a CIDI/DSM-III-R MDD, which led to the relative large 95% CI of the

prevalence of SCID/DSM-IV bipolar disorder in this group. Another limitation is that no respondents with other or no CIDI/DSM-III-R diagnoses were included. It may be argued that also among these subgroups SCID/DSM-IV bipolar disorders may be found, e.g. among respondents with CIDI/DSM-III-R depression NOS or psychotic disorders. Nevertheless, we assume that most respondents without a CIDI bipolar disorder but with a SCID bipolar disorder may be found among the respondents with a CIDI MDD, as probably most major depressive episodes are not missed by the CIDI.

Finally, in this study only respondents were interviewed and not their relatives. Hypomanic episodes are often experienced as ego-syntonic while family and significant others generally provide more reliable reports (Akiskal, 2002). Therefore, underdiagnosis of hypomania can occur in population studies where no information from significant others is collected (Angst et al., 2003). This was the case in NEMESIS and this follow-up study.

We conclude that compared to the SCID, the CIDI on the one hand overdiagnoses but on the other hand underdiagnoses bipolar disorder. This implicates that prevalence's of bipolar disorder based on fully structured interviews such as the CIDI should be interpreted with some caution. Our study suggests a lifetime prevalence of DSM-IV bipolar I disorder of around 2% and of bipolar spectrum disorder of 5%, which is much higher than often thought. It is however in line with findings in other studies.

References

Akiskal HS. Classification, diagnosis and boundaries of bipolar disorder. In: Maj M, Akiskal HS, Lopez-Ibor JJ, Satorius N (eds.), Bipolar Disorder, Wiley, London, 2002.

Angst J, Marneros A. Bipolarity from ancient to modern times: conception, birth and rebirth. J Affect Disord 2001;67:3-19.

Angst J, Gamma A. A new bipolar spectrum concept: a brief review. Bipolar Disord 2002;4 (Suppl.1):11-14.

Angst J, Gamma A, Benazzi F, Adjacic V, Eich D, Rössler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 2003;73:133-146.

Bijl RV, Zessen G van, Ravelli A. The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. Soc Psychiatry Psychiatr Epidemiol 1998;33:581-586.

Graaf R de, Bijl RV, Smit F, Ravelli A, Vollebergh WAM. Psychiatric and Sociodemographic Predictors of Attrition in a Longitudinal Study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Am J Epidemiol 2000; 152:1039-47.

Graaf R de, Bijl RV, Smit F, Vollebergh WAM. Predictors of first incidence of DSM-III-R psychiatric disorders in the general population: findings from the Netherlands Mental Health Survey and Incidence Study. Acta Psychiatr Scand 2002;106:303-313.

Have M ten, Vollebergh W, Bijl R, Nolen WA. Bipolar disorder in the general population. Prevalence, consequences and care utilisation: results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). J Affect Disord 2002;68:203-213.

Hirschfeld RM, Calabrese JR, Weissman MM, Reed M, Davies MA, Frye MA, Keck PE, Lewis L, McElroy SL, McNulty JP, Wagner KD. Screening for bipolar disorder in the community. J Clin Psychiatry 2003;64:53-59.

Hyler SE, Skodol AE, Kellman HD, Oldman JM, Rosnick L. Validity of the Personality Diagnostic Questionnaire-Revised: comparison with two structured interviews. Am J Psychiatry 1990;147:1043-1048.

Hyler SE. Personality Diagnostic Questionnaire –4+ (PDQ-4+). New York State Psychiatric Institute, New York, 1994.

Kessler RC, McGonagle KA, Zhao S. Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric Disorders in the United States. Arch Gen Psychiatry 1994;51:8-19.

Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med 1997;27:1079-1089.

Kessler R C, Wittchen HU, Abelson MA, McGonagle K, Schwarz N, Kendler KS, Knäuper B, Zhao S. Methodological studies of the Composite International Diagnostic Interview (CIDI) in the US National Comorbidity Survey (NCS). Int J of Methods in Psychiatr Res 1998;7:33-55.

O'Connell RA, Mayo JA, Sciutto MS. PDQ-R personality disorders in bipolar patients. J. Affect Disord 1991; 23:217-221.

Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health-Diagnostic Interview Schedule: Its history, characteristics and validity. Arch Gen Psychiatry 1981;38:381-389.

Robins LN, Locke BZ, Regier DA. An overview of psychiatric disorders in America. In: Robins LN, Regier DA (eds.), Psychiatric Disorders in America: The Epidemiologic Catchment Study, Free Press, New York, 1991.

Segal LD, Hersen M, Van Hasselt VB. Reliability of the Structured Clinical Interview for DSM-III-R: an Evaluative Review. Compr Psychiatry 1994;35:316-327.

Skre I, Onstad S, Torgerson S, Kringlen E. High interrater reliability for the Structured Clinical Interview for DSM-III-R Axis I (SCID-I). Acta Psychiatr Scand 1991;84:167-173.Spitzer LR,

Williams JBW, Gibbon M, First MB. The Structured Clinical Interview for DSM-II-R (SCID) I: History, Rationale, and Description. Arch Gen Psychiatry 1992;49:624-629.

Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual Framework and Item Selection. Med Care 1992;30:473-481.

Williams JBW, Gibbon M, First MB. The Structured Clinical Interview for DSM-II-R (SCID) II: Multisite Test-Retest Reliability. Arch Gen Psychiatry 1992;49:630-636.

Wittchen HU. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. J Psychiatr Res 1994;28:57-84.

World Health Organization. Composite International Diagnostic Interview (CIDI), Version 1.0. World Health Organization, Geneva, 1990.

CHAPTER 3

THE SOCIETAL COSTS AND QUALITY OF LIFE OF PATIENTS SUFFERING FROM BIPOLAR DISORDER IN THE NETHERLANDS

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Abstract

Objective

To assess the societal costs and quality of life of patients suffering from bipolar disorder in the Netherlands

Method

Forty persons with a lifetime diagnosis of bipolar disorder (SCID/DSM-IV) and representative for the Dutch general population were interviewed to collect data on direct (use of medical resources) and indirect (productivity losses due to absence from work and reduced efficiency at work) costs of illness. Respondents' quality of life was also assessed. Prevalence (5.2%) of bipolar disorder was used to estimate total costs.

Results

Total costs of bipolar disorder were estimated at US$1.83 billion (total direct costs=US$454 million; total indirect costs=US$1.37 billion). Participants' quality-of-life scores were lower than those of the general population.

Conclusion

The societal costs of patients suffering from bipolar disorder in the Netherlands were high, especially the indirect costs because of absence from work. The quality of life of bipolar patients was lower than the general population.

Key words: bipolar disorder, health care costs, indirect costs, quality of life

Introduction

Bipolar disorder is a psychiatric disorder characterised by the recurrent episodes of mania or hypomania and major depression. The lifetime prevalence is estimated between 2-5% (Angst et al., 2003).

A variety of medications are used to treat bipolar disorder. For years, lithium was the 'gold standard' in the treatment of bipolar disorder, but anticonvulsants, antidepressants and more recently (atypical) antipsychotics, either in monotherapy or in various combinations, have also been accepted as treatments in guidelines (Nolen et al., 2001; APA, 2002).

Despite the availability of various drug therapies, some patients with bipolar disorder never receive effective treatment. A study in the Netherlands indicated that 40% of people with bipolar disorder had never sought help for their emotional problems in the mental health care sector (ten Have et al., 2002). Persons who had never used mental health resources appeared to be less severely ill and experienced lower degrees of co-morbidity, especially co-occurring anxiety disorder (ten Have et al., 2002). Furthermore, patient non-compliance with drug therapy is a major issue in treating patients with bipolar disorder (Li et al., 2002). In the USA, reported non-compliance rates range from 51 to 64% (Keck et al., 1998). Moreover, two US studies indicated that the average time from illness onset to maintenance treatment was more than 8 years (Baldessarini et al., 1999; Kessler et al., 1998). A study on medical costs of bipolar disorder among patients in California concluded that direct health care costs were significantly higher for those patients who delayed the use of or did not use mood-stabilising agents during the first year of treatment (Li et al., 2002).

Several studies outside the Netherlands indicated that the costs of bipolar disorder to society are high (Li et al., 2002; Wyatt & Henter, 1995; Das Gupta & Guest, 2002; Stender et al., 2002). In 1991, the total costs of bipolar disorder were estimated at US$45 billion based on a 1.3% lifetime prevalence of bipolar disorder among adult Americans; approximately 85% of these costs were indirect (Wyatt & Henter, 1995). The indirect costs of bipolar disorder included US$20 billion in lost productivity of employed and unemployed patients with bipolar disorder, US$3 billion for lost productivity of institutionalised patients, US$6 billion for lost productivity of caregivers who provide care for family members with bipolar disorder and US$8 billion for productivity lost due to suicide (Wyatt & Henter, 1995). In the UK, the annual costs of bipolar disorder in were estimated at US$3 billion in 1998 (Das Gupta & Guest, 2002). Ten percent of these costs were attributable to the use of National Heath Service (NHS) resources, 4% to the use of non-medical resources and 86% to indirect costs (Das Gupta & Guest, 2002).

Zelicourt et al. (2003) published a study on the inpatient care costs of manic episodes in France for the year 1999. This study emphasised that a comparison of cost

estimates between countries may be hampered due to difference in patterns of medical care as well as methodological differences.

Recently, Kleinman et al. (2003) reported a review study on the cost of bipolar disorder and concluded that there were a few comprehensive cost-of-illness studies that focus primarily on bipolar disorder. Few data have been published on self-reported quality of life of patients with bipolar disorder (ten Have et al., 2002; Vojta et al., 2001). One study indicated that mania and hypomania are characterised by reduced, rather than increased, sense of well-being and quality of life among patients with bipolar disorder (Vojta et al., 2001). The socio-economic impact of patients suffering from bipolar disorder in the Netherlands is unknown.

Aims of the study

The aim of this study was to investigate the societal costs and quality of life of patients suffering from bipolar disorder in the Netherlands. Both direct costs (use of medical resources) and indirect costs (productivity losses due to absence from work and reduced efficiency at work) were calculated. We compared direct and indirect costs of the study participants who had previously used mental health resources with those who had not. In addition, health-related quality of life of the study participants was assessed and compared with that of the general population.

Material and methods

Study sample

Participants of this study were selected from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) sample. The NEMESIS was a study of mental health in a sample representative for the adult Dutch general population (Bijl et al., 1998; Bijl et al., 2002). A total of 7076 persons (aged 18 to 64) participated in the NEMESIS, which had three assessment points (T_0, T_1 and T_2) in 1996, 1997 and 1999 (Bijl et al., 2002). The primary diagnostic instrument in NEMESIS was the Composite International Diagnostic Interview 1.1 (CIDI) resulting in DSM-III-R diagnoses. One hundred and fifty eight respondents were identified with lifetime DSM-III-R diagnosis of bipolar disorder at any of the three assessments points. Of all 158 persons, 115 had participated in all three interviews, and 105 of them had indicated that they could be contacted in case of follow-up studies. Ultimately 74 (70.5%) of these 105 respondents participated in the current study, i.e. 46.8% of the total sample with a bipolar disorder. Clinicians re-interviewed these 74 respondents with the Structured Clinical Interview for DSM-IV (SCID) resulting in 30 cases (40.5%) fulfilling the DSM-IV criteria for bipolar disorder. In order to keep the interviewers blind for the original CIDI/DSM-III-R diagnosis, a second

group of 57 respondents with a lifetime diagnosis of unipolar major depressive disorder (MDD) was selected from the NEMISIS sample. These 57 were randomly selected out of all respondents with MDD (N=1403) from whom 1002 had participated in all three interviews, and 894 had agreed to participate in case of a follow-up study. Forty respondents (70%) participated in the study. Finally, 10 out of the 40 respondents (25%) with a CIDI/DSM-III-R diagnosis of a MDD met the DSM-IV criteria for bipolar disorder. The interviewers - a resident in psychiatry (ER) and a psychologist (MR) - were both intensively trained in the SCID. A senior psychiatrist (WN) was consulted in those cases (N=58, 50.9%) where the interviewers had any doubts how to rate specific symptoms relevant for a diagnosis. The corresponding adjusted lifetime prevalence in these groups was respectively 1 % (95% CI 0.7-1.3%) and 4.2% (95% CI 1.6%-6.9%). Hence, the prevalence of the SCID /DSM-IV bipolar disorder for persons aged 18–65 years in the Netherlands was estimated at 5.2% (95% C.I. 2.2–8.1) (Regeer et al., 2004).

As an addition to the above study, data on use of medical resources and health-related quality of life were collected during face-to-face interviews by the same interviewers. All respondents were interviewed at their home between August 2001 and February 2002.The Medical Ethical Review Board of the University Medical Center Utrecht approved the study. After the study was fully explained to the respondents, written informed consent was obtained from all respondents.

Direct and indirect costs

Direct costs were defined as the monetary valuation of the resources used to detect and treat medical problems. The indirect costs were defined as the productivity lost due to absence from work and reduced efficiency at work.

We used the 'Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness' (TiC-P) to collect data on direct and indirect costs (Hakkaart- van Roijen et al., 2002). The first part of the TiC-P consists of questions on the number of contacts with a general practitioner (GP), psychiatrist, medical specialists (that is, medical professionals working at a hospital), physiotherapist, alternative health practitioners, the day care/hospital length of stay, and the use of medication 4 weeks prior to the interview. Bottom-up methodology was used to calculate the total direct medical costs; that is, the total number of medical contacts (outpatient visits, hospital length of stay, use of medication, etc.) was multiplied by the 2002 unit prices of the corresponding health care service (Oostenbrink et al., 2000; CVZ, 2000). The reference unit prices of health care services for 1999 were adjusted to prices of 2002 by using the consumer price index, see table 3.1 (Oostenbrink et al., 2000; CBS, 2002). Additionally, the respondents were asked whether they had ever used mental health services.

The second part of the TiC-P includes a short form of the Health and Labour questionnaire (HLQ) for collecting data on productivity losses (van Roijen et al., 1996).

The respondents with a paid job were asked the number of hours and days they are employed per week. Additionally, information on their net income and occupation was collected. The Short-Form HLQ (SF-HLQ) consists of three modules that measure productivity losses: absence from work, reduced efficiency at work and difficulties with job performance (Dam et al., 1998). The days of absence from work and actual cost of hours missed at work due to health-related problems were assessed by the net income per day and per hour, respectively. The recall period for the SF-HLQ is 2 weeks. However, in case of long-term absence (over 2 weeks) the actual start date of the period of absence from work was asked. The friction-cost method was applied to assess the productivity losses. This method takes into account the economic circumstances that limit the losses of productivity to society, which is related to the fact that a formerly unemployed person may replace a person who becomes disabled (Koopmanschap & Rutten, 1996). The period needed to replace a worker (the so-called friction period) is estimated to be 5 months. Hence, the maximum indirect costs to society were confined to productivity losses during a densely period of 5 months. The number of lost working days per respondent was calculated taking into account the number of days and hours of paid employment per week.

Table 3.1 Unit costs for health services in the Netherlands, 2002

Service	Unit costs (in US$)	Source
General practitioner (GP)	17.38	Oostenbrink, 2000
Ambulatory mental health care	107.44	Calculated costs per contact on direct and indirect time spent by disciplines per contact (Hoeksma et al., 1995)
Psychiatric practice	70.92	Oostenbrink, 2000
Out-patient psychiatrist (general hospital)	58.94	Calculated costs per contact on direct and indirect time spent by disciplines per contact (Hoeksma et al., 1995)
Out-patient psychiatrist (psychiatric hospital)	82.84	Calculated costs per contact on direct and indirect time spent by disciplines per contact (Hoeksma et al., 1995)
Company doctor	17.38	Similar to the costs of a GP consult
Medical specialist	42.76	Calculated mean costs of contact with different medical specialists in the hospital
Physiotherapist	19.01	Oostenbrink, 2000
Social worker	46.58	Oostenbrink, 2000
Alternative health practitioner	45.74	Mean cost of visits for different alternative health practitioners
Medication	Cost/drug/mg	Dutch National Formulary

Absence from work

The first module of the SF-HLQ collects data on absence from work. Respondents with paying jobs were asked to indicate the number of days they had been absent from work in the 2 weeks preceding the interview. If the respondents were absent for the complete 2 weeks because of health-related problems, they were asked when this period of absence had started (long-term absence from work).

Reduced efficiency at work

To collect data on reduced efficiency at work, respondents with paying jobs were asked to estimate the number of extra hours they should have worked to compensate for productivity lost due to health-related problems.

Difficulties with job performance

We estimated an impediment score for assessing difficulties with performing both paying and non-paying jobs. Non-paying jobs were defined as household work shopping, childcare (in this context, taking care of one's own children), and odd jobs around the house. Individuals with paying jobs were asked to indicate the degree of impediment they experienced while performing their paying jobs. The response categories were: 0= no impediment, 1= some impediment and 2= a lot of impediment. The impediment score for a paying job ranged from 0 to 2.

Additionally, we applied a descriptive instrument of seven items to evaluate underlying problems causing reduced efficiency while performing a paying job and to calculate the efficiency score. The items were concentration, working pace, need to be alone, decision making, postponement of work, taking over work by others and other (the latter was an open-end question). Response modalities were: 1= never, 2= sometimes, 3= often and 4= always. The efficiency score for a paying job was calculated by adding up the scores for all seven items and ranged from 6 to 24.

For each category of a non-paying job (household work, shopping, childcare, odd jobs around the house), response categories and scores were comparable with those for a paying job: 0= no impediment, 1= some impediment and 2= a lot of impediment. The impediment score for a non-paying job was calculated by adding up the scores for four categories of non-paying jobs; the scores ranged from 0 to 8.

Estimating total costs of bipolar disorder in the Netherlands

When estimating the total annual costs of bipolar disorder in the Netherlands, we assumed that the costs incurred in the 4 weeks prior to the interview (direct medical costs) and 2 weeks prior to the interview because of short-term absence from work (indirect costs) were representative of the total year. The average direct costs were multiplied by 13 and the average indirect costs because of short-term absence by 26 to

calculate the annual costs. The annual costs due to long-term absence from work (over 2 weeks) were calculated by the total number of working days lost within the period of absence from work. The total direct costs of bipolar disorder in the Netherlands were calculated by multiplying the mean direct costs by the rate of bipolar disorder prevalence (5.2%) and the population of the Netherlands aged 18 to 64 as of 11 Otober 2002 (10 279 872) (CVZ, 2002; CBS, 2002). The total mean indirect costs per each respondent was calculated by multiplying mean indirect costs per each respondent with a paying job by the percentage of respondents having a paying job.

For reasons of comparison all costs were converted to US$ by using the mean exchange rate for 2002 of 1€=0,9456 US$.

Use of medical resources

We compared the use of medical resources among the respondents with the data from the Dutch national health databases (CBS, 2002). SF-HLQ scores of the study participants were compared with those of the general Dutch population (van Roijen et al., 1996).

Quality of life and self-perceived health status

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and the EuroQol: 5 Dimensions (EQ-5D) questionnaire were applied to assess the respondents' quality of life (Ware & Sherbourne, 1992; Essink-Bot et al., 1993). The SF-36 and EQ-5D are validated tools for measuring general health–related quality of life. The SF-36 consists of 36 items, assigned to domains of general health, physical functioning, role limitations (role-physical and role-emotional), social functioning, bodily pain, vitality and mental health. The EQ-5D consists of five items (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each having the rating of 'no problems', 'some problems' and 'extreme problems'. An interesting feature of the EQ-5D is the existence of a set of health-status preference values from a representative sample of the general population, which allows computing utilities. The quality-of-life scores of study participants (SF-36 and EQ-5D, respectively) were compared with those of the general population (Ware & Sherbourne, 1992; Essink-Bot et al., 1993). In addition, self-perceived health status was assessed with the Visual Analogue Scale (VAS), which scores range from 0 (worst imaginable health state) to 100 (best imaginable health state) (van Roijen et al., 1996).

Statistics

Statistical analysis was performed using the SPSS statistical software (version 10.1; SPPS Inc., Chicago, Illinois, USA). For comparison between groups, we applied one-way analysis of variance (ANOVA) using a significance level of $P < 0.05$. Continuous variables were compared using two-sided Student's *t*-test.

Results

Study participants

Table 3.2 presents the general characteristics of all 40 respondents with a SCID/DSM-IV diagnosis of bipolar disorder. Fifty percent of the respondents with no paying jobs indicated that they were unable to work due to health-related problems, compared with 12% in the general population (van Roijen et al., 1996).

Table 3.2 Characteristics of respondents with a SCID/DSM-IV diagnosis of bipolar disorder the Netherlands (N=40)

Characteristics	Values
Average age, years (mean SD)	43.84 (10.88)
Men, N (%)	15 (37.5)
Previous use of mental health resources, N (%)	13 (32.5)
Respondents with a paying job, N (%)	30 (75.0)
Paying job, mean (SD), hours per week	30.18 (8.46)
Net income per hour, (mean SD) US$	9.49 (3.50)
SCID/DSM-IV diagnosis	
Bipolar I diagnosis, N	14
Bipolar II diagnosis, N	14
Bipolar diagnosis NOS, N	7
Cyclothymia, N	3
Bipolar disorder, substance (antidepressant) induced, N	2

Direct costs

Table 3.3 presents mean direct medical costs per year incurred by the respondents (these costs are broken down by type of medical service and the percentage of respondents using a particular medical service). More than a half of the respondents (55%) used medications compared with 33% in the general population (CBS, 2002). Of the respondents using medications, 20.0% used sedatives, 7.7% used antidepressants, and 7.7% used lithium. Thirty percent of the respondents had a mean of 1.6 contacts with their GP in the 4 weeks prior to the interview. One eighth (12.5%) of the respondents contacted an alternative health practitioner more than once in the 4 weeks before the interview. Overall, 75% of the study participants generated the total direct costs. The mean direct medical costs were US$848.33 a year per person. The direct medical costs generated by respondents who had previously used mental health resources were significantly higher (US$1593; N=13) than those generated by respondents who had never used mental health resources (US$639; N=27) ($P$=0.007).

Table 3.3 Mean direct medical costs per year incurred by respondents with a SCID/DSMIV diagnosis of bipolar disorder in US$ (N=40)

Type of (medical) service	Per year	Percentage of the total direct medical costs	Respondents using the service, N (%)
General practitioner	107.26	13	12 (30)
Ambulatory mental health care	69.79	8	2 (5)
Psychiatric practice	69.15	8	3 (7.5)
Out-patient psychiatrist (general hospital)	51.78	3	3 (7.5)
Out-patient psychiatrist (psychiatric hospital)	15.13	2	1 (2.5)
Company doctor	5.65	1	1 (2.5)
Medical specialist*	180.66	21	4 (10)
Physiotherapist	74.13	9	4 (10)
Social worker	45.42	5	2 (5)
Alternative health practitioner	108.67	13	5 (12.5)
Medication	120.68	14	22 (55)
Total	**848.33**	**100**	**30 (75)**

** Any medical professional working at a hospital.*

The total number has been rounded.

Indirect costs

Absence from work

Table 3.4 presents indirect cost data for respondents with a paying job. More than a quarter of the respondents with a paying job (26.7%; eight of 30) were absent from work due to health-related problems in the 2 weeks preceding the interview. In addition, 16.7% (five of 30) of the respondents with a paying job were absent from work for more than two weeks before the interview. However, the period of absence was less than 2 months for all these respondents. Thus, this period was much shorter than the friction period of 5 months; therefore, all productivity lost during absence from work was counted as indirect costs. The mean annual number of days of absence from work was 55.5 per each respondent with a paying job. This is significantly higher than the mean annual number of approximately 13 days of absence from work for the general population of the Netherlands (P=0.007) (van Roijen et al., 1996). The mean indirect costs because of absence from work were more than twice as high for the respondents who had previously used mental health resources compared with those who had never used such resources before the interview (US$5117 and US$2404, respectively).

Table 3.4 Mean number of days lost due to absence from work and reduced efficiency per year and mean indirect costs of bipolar disorder for persons with a paying job (N=30)

Type of Indirect Cost	Days	Costs (US$)
Absence from work	55.5	3037.15
Reduced efficiency at work	7.7	395.03
Total	63.2	3432.19

Reduced efficiency at work

The mean productivity loss associated with reduced efficiency at work equalled 7.7 days per year (table 3.4). However, these losses of productivity were not significantly different from the 1.3 days of productivity lost due to reduced efficiency in the general population (P=0.108) (van Roijen et al., 1996). The mean indirect costs associated with reduced efficiency of respondents with a paying job were more than US$378 per year. Unlike the indirect costs due to absence, the indirect costs due to reduced efficiency were much lower in the group of study participants who had previously used mental health resources (US$19; SD US$51) compared with those who had never used such services (US$520; SD US$1352).

Difficulties with job performance

Nearly forty percent (38.5%) of the study participants indicated that they experienced some difficulties while performing a paying job due to health-related problems. The impediment score associated with paying jobs was 0.37 for study participants compared with 0.32 for the general population (P=0.599; not a statistically significant difference) (van Roijen et al., 1996).

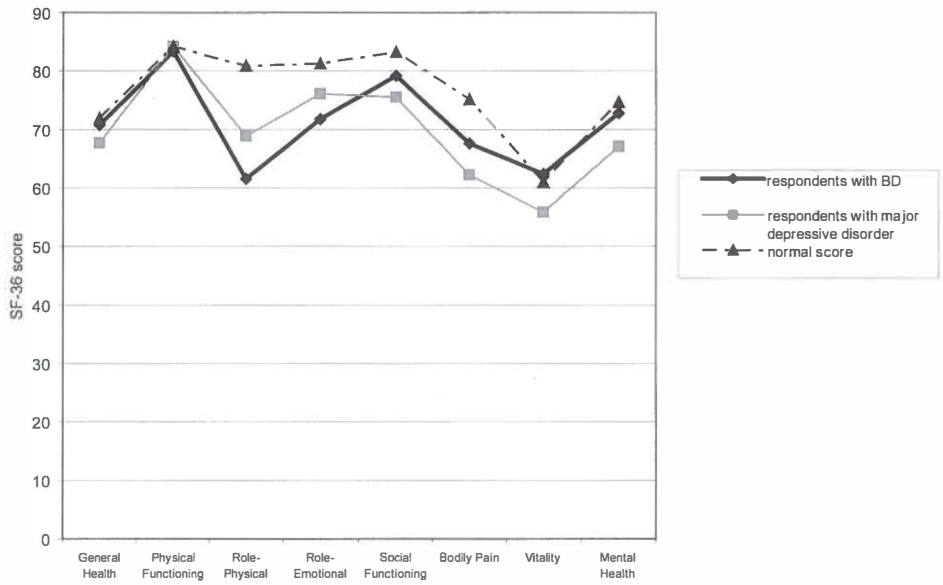
Approximately one quarter (23.3%) of the respondents indicated that they sometimes experienced problems with concentration, which affected their job performance. Approximately 16.7% (five of 30) of study participants who had a paying job indicated they had to slow down their working pace and had problems making decisions at work. The resulting efficiency score for respondents with paying jobs was 7.36 (SD 2.56) compared with 6.7 (SD 1.37) for the general population (van Roijen et al., 1996), suggesting that patients with bipolar disorder experienced slightly more problems performing their jobs.

Approximately 36.0% of the respondents indicated that they experienced problems performing non-paying jobs (e.g., household work). The total impediment score for non-paying jobs was 1.13 (SD 1.82) compared with that of 1.43 (SD 2.2) for the general population (van Roijen et al., 1996). The difference between the impediment scores associated with non-paying jobs among study participants and those of the general Dutch population was not significant (P=0.308).

Total costs of bipolar disorder in the Netherlands

The total mean indirect costs per respondent with a paying job were US$3432.19 per year. The total direct and indirect costs of bipolar disorder in the Netherlands for persons between 18 and 64 years were calculated to be 0.052 * 10 279 872 * (US$848.33 + (0.75 * US$3432.19)) = US$1.83 billion; that is, prevalence of bipolar disorder in the Netherlands * population of the Netherlands aged 18–65 as of 11 October 2002 * (mean direct cost per respondent + (percentage of respondents with a paying job * mean indirect cost per respondent)).

Figure 3.1 Mean SF-36 scores of the respondents SCID DSM-IV diagnosis of bipolar disorder (N=40) compared with the general population in the Netherlands.



SF-36=Medical Outcomes Study 36-Item Short-Form Health Survey
BD=bipolar disorder

Quality of life and self-perceived health status

When the societal preference values were applied to the EQ-5D scores of the study participants, a mean utility score of 0.82 was calculated (SD 0.20). This score was not significantly different from the EQ-5D score of the general population (0.88; *P*=0.084) (Dam et al., 1998; Kessler et al., 1997).

The mean score for self-perceived health status (measured by using the VAS) was 77.18 (SD 16.77). Here, the study participants scored significantly worse compared with the general population (84.2; *P*=0.013).

Figure 3.1 presents mean SF-36 scores of the study participants compared with normal SF-36 scores (that is, scores for the general population). Respondents with SCID/DSM-IV bipolar disorder scored significantly lower on role-physical SF-36 score (P=0.010). This could not be explained by correcting for two persons who indicated that they visited a surgeon or orthopaedist in the preceding 4 weeks. The SF-36 scores did not significantly differ between study participants who had previously used mental health resources and those who had not. A comparison of the SF-36 scores of the respondents with bipolar disorder with those of the NEMESIS participants (at three assessment points) did not show significant differences. However, respondents with bipolar disorder had lower role-physical scores than the NEMESIS participants.

Discussion

Based on the 5.2% prevalence of bipolar disorder in the Netherlands (Regeer et al., 2004), the total annual costs of bipolar disorder in the Netherlands were estimated at US$1.83 billion. Seventy-five percent of the total costs of bipolar disorder in the Netherlands were due to indirect costs, which is somewhat lower than the figures from studies elsewhere in the world (Wyatt & Henter, 1995; Das Gupta & Guest 2002). Less than half (40.5%) of the respondents with a DSM-III-R bipolar disorder based on the CIDI also fulfilled DSM-IV criteria for bipolar disorder when interviewed with the SCID. Our finding that among respondents with a CIDI/DSM-III-R bipolar I disorder only 22% also had a SCID/DSM-IV bipolar I disorder, is comparable to the 28%, which was found in the reappraisal study of Kessler et al. (1997). The study of Regeer et al. found that the prevalence of bipolar disorder is overdiagnosed as well as underdiagnosed by the CIDI (Regeer et al., 2004). The latter by patients with a CIDI major depressive disorder. One of the possible explanations for this may be failing to diagnose a manic or hypomanic episode in patients who present primarily with depressive episode, which leads automatically to the diagnosis major depressive disorder. This is in line with clinical impressions that especially in these patients the diagnosis bipolar II disorder is missed (Gamma et al., 2003). In accordance with other studies on the costs of illness of bipolar disorder our study indicated that indirect costs because of production losses were much higher than the direct medical costs. So, not including the indirect costs would underestimate the costs to society of bipolar disorder. The indirect costs in our study were attributed mainly to absence from work (rather than reduced efficiency at work). Compared with the general population, study participants did not have a higher impediment score associated with performing paying or non-paying jobs.

Table 3.5 presents an overview of the methods and main results of four international studies on the costs of bipolar disorder. The applied methodology

differs among the studies. All studies (except ours) estimated direct costs by assigning national figures to costs of bipolar disorder, using the so-called 'Top-Down Method'. Furthermore, Wyatt and Henter (1995) and Das Gupta and Guest (2002) applied the human capital approach for calculating indirect costs, which estimates the value of productivity potentially lost as a consequence of a disease. According to the human capital method, in case of patient's disability or premature death at a specific age, the total productivity losses from that age to the retirement age are counted as indirect costs. This approach contradicts the friction cost method, which seeks to estimate the real costs of disease to society (Koopmanschap et al., 1995).

Furthermore, the definitions of the prevalence and diagnosis of bipolar disorder, as well as direct and indirect costs associated with this illness, varied among the studies. Our study is the only study that defined bipolar disorder using the SCID/DSM-IV criteria based on a semi-structured interview (SCID) by trained clinicians. Regarding costs, Wyatt and Henter (1995) and Das Gupta and Guest (2002) included direct *non*-medical costs of bipolar disorder in their analyses (such as costs associated with the criminal justice system and use of social services). As far as indirect costs are concerned, Wyatt and Henter (1995) included the following in their analyses (in addition to productivity losses of patients with manic-depressive illness): productivity losses of caregivers who provide care for family members with manic-depressive illness and productivity lost due to suicide. Finally, the studies for the USA assessed the costs of illness for 1991 and 1996 and treatment of bipolar and the associated costs may have changed over time. Overall, inconsistent definitions of bipolar disorder and its prevalence, as well as different methodology used throughout these studies, impede the comparison of their results (that is, costs of bipolar disorder to society).

Our study had several limitations. We had only one assessment point per respondent to estimate the annual per-person costs of bipolar disorder and respondents' quality of life. The recall periods for the use of medical services and productivity losses were 4 and 2 weeks, respectively. Some studies have indicated that more accurate results are obtained with longer recall periods (Harlow & Linet, 1989; Linet et al., 1989; Heliovaara et al., 1993). The episodic character of bipolar disorder may have an impact on the costs, e.g. an episode may lead to a hospital admission. A study in the UK indicated that costs because of hospital admissions was responsible for 35% of the direct medical costs (Das Gupta & Guest 2002). The respondents included in our study may be less severe patients, as we did not found costs for hospitalisation. It is expected that more severe cases were underrepresented in our study because they may be admitted to a hospital or refused to participate in the study because of their health status at the time of the study. Hence, this would underestimate the mean costs of illness per patient.

The indirect costs are responsible for the main part of the total costs (75%). With

respect to long-term absence from work (over 2 weeks) we had additional information when the period of absence started, e.g. the actual long-term period of absence form work. Nearly 40% (five of 13) of the respondents was absent from work for a period longer than 2 weeks. For these respondents the real recall period was determined by the start of the period of absence. Hence, a significant part of the total costs was calculated on a much longer recall period than the standardized recall of 2 weeks for other parts of the HLQ.

We assumed that the direct medical costs incurred in those 4 and 2 weeks in case of short-term absence for work were representative for the whole year. We used the following to validate this assumption: First, our estimates of the proportion of direct and indirect costs were similar to other studies on the costs of bipolar disorder conducted outside the Netherlands (Li et al., 2002; Wyatt & Henter, 1995; Das Gupta & Guest 2002), which used data from national health care databases. Secondly, the TiC-P interview provided data regarding the previous use of mental health care resources by the study participants. The results of the NEMESIS showed that people with psychiatric disorders who use mental health care resources are generally more severely ill (ten Have et al., 2002). Hence, this group of patients was expected to have higher direct and indirect costs, which was confirmed by our study. Thirdly, indirect costs due to absence from work were relatively high for study participants with previous use of mental health resources compared with those who had not used such resources. The latter group of respondents, however, generated relatively high indirect costs due to reduced efficiency at work. This suggests that patients who had previously used mental health resources were more severely ill and had to be absent from work because of health-related problems. On the contrary, study participants without previous use of mental health resources may have less severe health problems, which result in decreased efficiency at work (rather than absence from work). Absence from work and reduced efficiency at work may be interpreted as complementary items.

Another limitation of the study was that questions regarding the use of medical resources and productivity losses were not specific to bipolar disorder, but referred to health-related problems in general. Because of the symptoms of bipolar disorder, patients cannot easily distinguish between problems related to bipolar disorder itself and other mental health problems and/or general health problems. This may lead to the costs of bipolar disorder being overestimated. However, our study sample did not include severely ill in-patients with bipolar disorder, which might have underestimated the total costs of bipolar disorder in the Netherlands.

Overall, the impediment scores for both paying and non-paying jobs were comparable between the study participants and the general population. On the one hand, this may indicate that functioning of this group of patients with bipolar disorder was comparable with that of the general population. On the other hand, these

results may indicate that study participants did not experience difficulties with job performance because of their coping skills. Furthermore, the instrument we used for assessing difficulties with job performance may not be sensitive enough to measure these differences.

Finally, the study population was small; consequently, calculated costs remain uncertain and differences in costs and quality of life versus other populations had to be large to be significant. The same explanation may be applicable to the assessment of the quality of life. According to the scarce literature (ten Have et al., 2002; Vojta et al., 2001) on quality of life of patients with bipolar disorder, such patients experience decreased quality of life because of health-related problems. A future quality-of-life study of patients with bipolar disorder should include diagnosis-specific quality-of-life instruments as well as generic health-rating instruments.

The cost-of-illness estimates cannot be interpreted as the savings to be achieved with new successful medical interventions. However, results of a cost-of-illness study may provide helpful information for designing a cost-effectiveness study. On the one hand, cost-of-illness data can be used to indicate which cost items and quality-of-life parameters should be included in the cost-effectiveness study. On the other hand, the results of a cost-of-illness study may be used for estimating the cost-effectiveness ratio of an intervention. For instance, the estimates of productivity losses in certain patient groups may help estimate the reduction of indirect costs as a consequence of a successful intervention.

Overall, the societal costs of bipolar disorder in the Netherlands were high, especially the indirect costs due to absence from work. Furthermore, the quality-of-life scores of the study participants and their self-perceived health status were lower than those of the general population.

Table 3.5 Overview of international studies on costs of bipolar disorder

Study Characteristics	Name of Study			
	Wyatt and Henter (1995)	**Stender et al. (2002)**	**Das Gupta and Guest (2002)***	**Hakkaart et al.** (present paper)**
Country	USA (nationwide)	USA (north-eastern states)	UK	The Netherlands
Year	1991	1996	1998	2002
Methodology				
Direct costs	Top-down	Top-down	Top-down	Bottom-up
Indirect costs	Human capital		Human capital	Friction cost
Diagnosis	Bipolar disorder (DSM-III-R)	Bipolar disorder (ICD-9 296.0–296.8)	Hypomania/mania; other manic-depressive psychoses; affective psychosis (ICD-10 F31.0–F31.9)	Bipolar disorder (SCID / DSM-IV)
Study sample	50 states, the District of Columbia, and five United States territories	3120	1807	40
Data	National databases	A New England insurer database	National databases, expert opinion	Questionnaire (TiC-P)
Prevalence	1.3%	n.a.	1.0–2.5%	5.2%

Study Characteristics	Name of Study			
	Wyatt and Henter (1995)	**Stender et al. (2002)**	**Das Gupta and Guest (2002)***	**Hakkaart et al.** (present paper)**
Definition of direct costs	Treatment-related costs of in-patient and out-patient care; non-treatment-related costs (e.g., for criminal justice system expenditures)	Medical costs (preventive medicine, out-patient visits, psychotherapeutic care, hospital admissions, etc.)	Medical costs (using services of a general practitioner, hospital admissions, etc.) and direct non-medical costs (such as using social services, the criminal justice system, etc.)	Direct medical costs
Definition of indirect costs	Lost productivity of paid and unpaid workers; institutionalised manic-depressive patients; manic-depressive persons who had committed suicide; and caregivers of family members with manic depression	n.a.	Excess unemployment, absence from work, suicide	Absence from work and reduced efficiency at work
Total annual direct costs	US$7.57 billion	n.a.	US$429 million	US$454 million
Costs per patient	n.a.	(US$5202)	(US$1444)	(US$848)
Indirect costs	US$37.6 billion	n.a.	US$2.66 billion	US$1.37 billion
Costs per patient	n.a.	n.a.	(US$8963)	(US$3432)

n.a.= not available.

** The costs are converted from Pound Sterling by the mean exchange rate for 2002 of 1£= 1,50US$*

***The costs are converted from euros to US$ based by the mean exchange rate for 2002 of 1€=0,9456 US$*

References

Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rossler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 2003;73:133-146.

APA. Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry 2002;159(Suppl. 4):1-50.

Baldessarini RJ, Tondo L, Hennen J. Treatment delays in bipolar disorders. Am J Psychiatry 1999;156:811-812.

Bijl RV, van Zessen G, Ravelli A, de Rijk C, Langendoen Y. The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. Soc Psychiatry Psychiatr Epidemiol 1998;33:581-586.

Bijl RV, De Graaf R, Ravelli A, Smit F, Vollebergh WA. Gender and age-specific first incidence of DSM-III-R psychiatric disorders in the general population Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 2002;37:372-9.

CVZ HIC. Pharmaceutical compass. Amstelveen: CVZ HIC, 2002.

CBS. http://www.cbs.nl. In: Central Bureau for Statistics, 2002 (accessed on 11 October 2002).

Dam QD van, Spijker Avt, Arends LR, Roijen LH-v, Donker MCH, Trijsburg RW. Costeffectiveness of psychotherapy: A feasibility study (in Dutch). Tijdschrift voor Psychotherapie 1998;24:5-22.

Das Gupta R, Guest JF. Annual cost of bipolar disorder to UK society. Br J Psychiatry 2002;180:227-233.

Essink-Bot ML, Stouthard ME, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQolc-questionnaire. Health Econ 1993;2:237-246.

Hakkaart- van Roijen L. Manual Trimbos/iMTA questionnaire for costs associated with psychiatric illness (in Dutch). Rotterdam: institute for Medical Technology Assessment; 2002.

Harlow SD, Linet MS. Agreement between questionnaire data and medical records. The evidence for accuracy of recall. Am J Epidemiol 1989;129:233-248.

Have MTten, Vollebergh W, Bijl R, Nolen W. Bipolar disorder in the general population. Prevalence, consequences and care utilisation. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). J. Affective Disorders 2002;68:203-213.

Heliovaara M, Aromaa A, Klaukka T, Knekt P, Joukamaa M, Impivaara O. Reliability and validity of interview data on chronic diseases. The Mini-Finland Health Survey. J Clin Epidemiol 1993;46:181-191.

Hoeksma B, Bastings I, Lange HD, Meij RD. Time spent in MHC and outpatient psychiatric hospitals (in Dutch). Hoeksma, Homans and Menting, Enschede, 1995.

Keck PE, Jr., McElroy SL, Strakowski SM, West SA, Sax KW, Hawkins JM, Bourne ML, Haggard P. 12-month outcome of patients with bipolar disorder following hospitalization for a manic or mixed episode. Am J Psychiatry 1998;155:646-652.

Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med 1997;27:1079-1089.

Kessler RC, Olfson M, Berglund PA. Patterns and predictors of treatment contact after first onset of psychiatric disorders. Am J Psychiatry 1998;155:62-69.

Kleinman L, Lowin A, Flood E, Gandhi G, Edgell E, Revicki D. Costs of bipolar disorder. Pharmacoeconomics 2003;21:601-622.

Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ 1995;14:171-189.

Koopmanschap MA, Rutten FF. A practical guide for calculating indirect costs of disease. Pharmacoeconomics 1996;10:460-466.

Li J, McCombs JS, Stimmel GL. Cost of treating bipolar disorder in the California Medicaid (Medi-Cal) program. J Affect Disord 2002;71:131-139.

Linet MS, Harlow SD, McLaughlin JK, McCaffrey LD. A comparison of interview data and medical records for previous medical conditions and surgery. J Clin Epidemiol 1989;42:1207-1213.

Nolen W, Klein EK-vd, Honig A, Bouvy P, Klompenhouwer J, Witt AD, et al. The Dutch Psychiatric Association's Guidelines for the Management of Bipolar Disorders (in Dutch)[Richtlijn bipolaire stoornis]. Boom Publishers, Amsterdam, 2001.

Oostenbrink JB, M.A. Koopmanschap, F.F.H. Rutten. Manual for research on costs (in Dutch). Amstelveen: College for Health Insurance's (CVZ); 2000.

Regeer EJ, ten Have M, Rosso ML, Hakkaart-van Roijen L, Vollebergh W, Nolen WA. Prevalence of bipolar disorder in the general population: a Reappraisal Study of the Netherlands Mental Health Survey and Incidence Study. Acta Psychiatr Scand 2004;110:374-382.

Roijen L van, Essink-Bot ML, Koopmanschap MA, Bonsel G, Rutten FF. Labor and health status in economic evaluation of health care. The Health and Labor Questionnaire. Int J Technol Assess Health Care 1996;12:405-415.

Stender M, Bryant-Comstock L, Phillips S. Medical resource use among patients treated for bipolar disorder: a retrospective, cross-sectional, descriptive analysis. Clin Ther 2002;24:1668-1676.

Vojta C, Kinosian B, Glick H, Altshuler L, Bauer MS. Self-reported quality of life across mood states in bipolar disorder. Compr Psychiatry 2001;42:190-195.

Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-483.

Wyatt RJ, Henter I. An economic evaluation of manic-depressive illness--1991. Soc Psychiatry Psychiatr Epidemiol 1995;30:213-219.

Zelicourt M de, Dardennes R, Verdoux H, Gandhi G, Khoshnood B, Chomette E, Papatheodorou ML, Edgell ET, Even C, Fagnani F. Frequency of hospitalisations and inpatient care costs of manic episodes: in patients with bipolar I disorder in France. Pharmacoeconomics 2003;21:1081-1090.

CHAPTER 4

A PROSPECTIVE STUDY OF THE TRANSITION RATES OF SUBTHRESHOLD (HYPO)MANIA AND DEPRESSION IN THE GENERAL POPULATION

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Abstract

Background

Previous work suggests that subthreshold depression and subthreshold (hypo)mania are common, however little is known about prognosis in terms of transition to clinical disorder. The current paper presents data on the temporal relationship between subthreshold and clinical expression of mood phenotypes.

Method

In a random general population sample of 7076 individuals, symptoms of depression and (hypo)mania were measured with the CIDI at baseline, after one year, and two years later.

Results

At baseline, the lifetime prevalences of depressive and (hypo)manic symptoms were 17.2% and 1.2%, respectively. Predictive values of mood symptoms for a DSM-III-R mood disorder ranged from 14.3% to 50%. (Hypo)manic mood symptoms had much higher predictive values than unipolar manifestations, not only for bipolar disorder, but also for major depression.

Conclusions

The subthreshold expressions of depression and (hypo)mania are prevalent and continuous with more severe clinical states. The cross-prediction of mood symptoms may support a continuum from depressive to (hypo)manic symptoms. The high predictive value of (hypo)manic symptoms for mood disorders suggests that the experience of (hypo)manic symptoms is a stronger indicator of vulnerability for mood dysregulation than the experience of depressive symptoms.

Introduction

Subthreshold depression and (hypo)mania, defined as experiencing a distinct period of depressive or (hypo)manic symptoms without fulfilling the DSM-III-R/IV diagnostic criteria for a mood disorder, are common and highly relevant in terms of health service use, quality of life and impairment (Angst & Merikangas, 1997; Judd et al., 2002; Angst et al., 2003*a*; Cuijpers & Smit, 2004; Cuijpers et al., 2004). Prevalences of up to 13 and 8.9 % have been reported for subthreshold depression and subthreshold (hypo)mania, respectively (Angst & Merikangas, 1997; Angst et al., 2003*a*), adding credence to the suggestion that multifactorial disorders such as bipolar disorder and major depression are distributed in populations as continua, only some of which comes into contact with mental health services. The superimposition of a categorical diagnostic classification on a continuously distributed trait may thus lead to a diagnostic system that fails to represent adequately the underlying continuum of the symptoms of a disease (Angst & Merikangas, 1997; Kendler & Gardner, 1998; Johns & van Os, 2001; Akiskal, 2002; Angst et al., 2003*a*; Judd & Akiskal, 2003). Similarly, the unipolar-bipolar distinction has also been challenged. A study by Cassano et al. (2004) showed a significant number of (hypo)manic symptoms in patients with recurrent major depression, and Benazzi and Akiskal (2003) reported a prevalence of (partially) subcategorial hypomania, defined as with a duration of more than two days, in 61.3 % of depressed outpatients. Similarly, Angst and Gamma (2002) calculated that if a broader definition of hypomania were applied, half of all the cases of major depressive disorders would be classified as bipolar.

Given the likely existence of a continuous distribution of mood symptomatology with graded impact on functioning and well-being, the study of transitions from one position of the continuum to another becomes relevant, in particular with respect to the diagnostic relationship between the subthreshold and clinical domains over time. Relatively little is known about the prognosis of subthreshold mood disorder in terms of transition to a DSM-III-R disorder (Judd & Akiskal, 2003). For bipolar disorder, the only known prospective data are those of the Oregon Adolescent Depression Project by Lewinsohn et al. (2000; 2003) which despite small sample sizes suggested predictive value of manic symptoms for developing major depressive disorders, anxiety disorders and suicidal behaviour but not for bipolar disorder. Prospective studies of subthreshold depression have shown an increased risk of future major depressive episodes (Angst & Merikangas, 1997; Cuijpers & Smit, 2004; Cuijpers et al., 2004). Angst and Merikangas (1997) reported that 29% of the respondents with subthreshold depression in the Zurich Cohort Study of Young Adults developed a major depressive disorder during the follow-up period. Early detection and intervention of mood disorders may be entertained in the light of the kindling hypothesis, which posits that mood episodes may leave residual

traces and vulnerability to further occurrences of mood episodes (Post, 1992). There is a powerful rationale for early intervention in severe mental illness such as bipolar disorder (Goodwin & Ghaemi, 1998) and recent studies have found evidence that it may be possible to prevent the development of a major depressive disorder by intervening in people with subthreshold depression (Cuijpers & Smit, 2004).

The aim of the current study, therefore, was to assess the relationship between the subthreshold and clinical expression of mood phenotypes over time, expressed as likelihood ratios (diagnostic usefulness) and post-test probabilities (predictive value).

Method

Sample

The Netherlands Mental Health Survey and Incidence Study (NEMESIS), is a prospective study with three assessment points over a period of 3 years (Bijl et al., 1998*a, b*). A multistage, stratified, random sampling procedure was used to first select 90 municipalities, then a sample of private households, and finally a Dutch-speaking individual aged 18-64 years within each household. Selected households were sent an introductory letter by the Minister of Health, inviting them to participate. A total of 7076 individuals was interviewed at baseline, representing a response rate of 69.7%. At T_1 (one year post-baseline), 5618 respondents participated for the second time; at T_2 (three years post-baseline), 4848 respondents participated. The sample was found to be representative of the Dutch population in terms of gender, marital status and level of urbanisation (Bijl et al., 1998a), with the exception of a slight underrepresentation of individuals in the age group 18-24 years. Examination of attrition suggested that, after adjustment for influences of demographic variables, this had occurred largely independent of the variable of interest: mental health (de Graaf et al., 2000). As this was a study of relative rather than absolute risk, no poststratification weightings were applied to the data. NEMESIS was conducted with the approval of the Internal Review Board of the Trimbos Institute and after oral explanation of the study, in addition to the introductory letter, all respondents gave verbal consent to participate in the study (written consent was not obligatory in The Netherlands at the time of the study).

Instruments

Respondents were interviewed at home by different interviewers at the three assessment points. The Composite International Diagnostic Interview (CIDI) version 1.1 (Robins et al., 1988; WHO, 1990; Smeets & Dingemans, 1993) was used, yielding DSM-III-R diagnoses. The CIDI was designed for trained interviewers who are not clinicians and has been found to have high interrater reliability (Wittchen et al., 1991; Cottler et al.,

1991), and high test-retest reliability (Semler et al., 1987; Wacker et al., 1990; Wittchen, 1994). Ninety interviewers experienced in systematic data collection collected the data, having received a 3-day training course in recruiting and interviewing, followed by a 4-day course at the WHO-CIDI training centre in Amsterdam. Extensive monitoring and quality checks took place throughout the entire data collection period (Bijl et al., 1998*a*). The interviewers and the respondents were kept blind with respect to previous diagnoses at all three assessment points

Mood diagnoses and assessment of mood symptoms

At baseline, the presence of any lifetime depressive or (hypo)manic symptom and the total number of lifetime depressive and (hypo)manic symptoms were assessed with the 28 items of the CIDI depression and dysthymia section (E) and the 11 items of the CIDI mania section (F) (for details see Krabbendam et al., 2004). All these items can be rated either "yes" (1) or "no" (0). The depressive symptom has to be present for at least 2 weeks and the (hypo)manic symptom has to be present for at least 2 days. The depression and dysthymia section starts with assessing the presence of depressive mood and/or anhedonia, the mania section starts with assessing the presence of abnormally and persistently elevated, expansive or irritable mood. Secondly, all other associated depressive and (hypo)manic symptoms are assessed. To establish a DSM-III-R diagnosis of a mood disorder the CIDI assesses to what degree the mood symptoms and the other symptoms were experienced in the same time period. The resulting depression and (hypo)mania symptom scores can be considered as the psychometric expression of affective load, and its polarity, of a person over a certain time period. The lifetime measures of depressive or (hypo)manic symptoms at baseline are referred to hereafter as lifetime depressive symptoms and lifetime (hypo)manic symptoms, respectively. At T_1 and T_2, the CIDI depression and dysthymia section and mania section were used to make a DSM-III-R diagnosis of incident major depression or incident bipolar disorder [bipolar I disorder and bipolar disorder not otherwise specified (NOS)], hereafter referred to as post-baseline major depression and post-baseline bipolar disorder, respectively.

Data analysis

Diagnostic predictive value

In the predictive analyses, the test variable was the dichotomous presence or absence of one or more lifetime depressive or lifetime (hypo)manic symptoms at baseline *without* any lifetime diagnosis major depression or bipolar disorder. Post-baseline onset of major depression and bipolar disorder was analysed in relation to the test variable of lifetime depressive symptoms and lifetime (hypo)manic symptoms by calculating post-test probabilities (PPs) with the DIAGTEST procedure in the STATA statistical program, version 8 (StataCorp, 2002). The PP is the likelihood of disease (post-baseline

mood disorder) given a positive test result (lifetime mood symptoms), calculated as the proportion of individuals with lifetime mood symptoms who had developed post-baseline mood disorder: PP = pr (disease / positive test) (Sackett et al., 1997).

In order to examine the degree of linearity of the predictive function, analyses were conducted according to number of symptoms. Given the smaller numbers in these cells and the cross-prediction of lifetime depressive and (hypo)manic symptoms (see below), a combined outcome of post-baseline mood disorder was used, including both major depression and bipolar disorder.

Diagnostic usefulness

Apart from the predictive function, another measure of diagnostic usefulness was calculated: the diagnostic likelihood ratio (LR). The LR, or how much more likely it is that a positive test result (lifetime mood symptom) is seen in those with as opposed to those without the disease (in this case post-baseline mood disorder) in question, is the traditional measure of diagnostic value (calculated as the proportion of true positives (=sensitivity) divided by the proportion of false positives (=1-specificity)): Likelihood ratio = sensitivity / (1-specificity). A test with a likelihood ratio of 10 (i.e. 10 times more likely to be a true rather than a false positive) is generally considered useful (Sackett et al., 1997). This test in fact measures the degree of overlap between lifetime mood symptoms and post-baseline mood diagnoses.

Risk set

The risk set (i.e. the set of individuals at risk of developing the post-baseline outcomes of major depression and bipolar disorder) consisted of i) all individuals who at baseline had never had any diagnosis of a) major depression (baseline lifetime prevalence: N=1164, 16.5%) *and* never had any diagnosis of b) bipolar disorder (baseline lifetime prevalence: N=132, 1.9%) (ten Have et al., 2002) and ii) all individuals who had had at least one post-baseline CIDI interview (T_1 or T_2). After applying these criteria, the risk set consisted of 4628 individuals.

Results

The mean age of the risk set was 41.2 years, 49% were men. The 3 years post-baseline incidence of major depression was 5.5% (N=255), and the 3 years post-baseline incidence of bipolar disorder was 0.3% (N=14). The proportion of individuals at baseline without lifetime DSM-III-R mood disorders but with any number of lifetime depressive symptoms was 17.2% (N=797), the number of symptoms in these 797 individuals ranged from 2 to 26 (median: 7). The proportion of individuals at baseline without DSM-III-R mood

disorders but with any number of lifetime (hypo)manic symptoms was 1.2% (N=56), the number of symptoms in these 56 individuals ranged from 3 to 9 (median: 4).

Post-test probabilities and likelihood ratio major depression

Table 4.1 lists the PPs and likelihood ratios of lifetime depressive or lifetime (hypo)manic symptoms for developing a post-baseline major depression. The PP of developing post-baseline major depression given the presence of lifetime depressive symptoms was 13.6% (108 out of 797), which was considerably higher than the probability of developing major depression in the group without evidence of subthreshold depression (3.8%; 147 out of 3831). The diagnostic overlap expressed as likelihood ratio was 2.7 (95% CI: 2.3-3.2). Similarly, the PP of developing post-baseline major depression given the presence of lifetime *(hypo)manic* symptoms was 17.9% (10 out of 56), which was considerably higher than the probability of developing major depression in the group without evidence of subthreshold (hypo)mania (5.4%; 245 out of 4573). The diagnostic overlap expressed as likelihood ratio was 3.7 (95% CI: 1.9-7.3).

Table 4.1 Post-test probabilities and likelihood ratio of lifetime depressive and lifetime (hypo)manic symptoms at baseline for post-baseline major depression at T_1 or T_2

Lifetime symptoms	Post-baseline major depression
PP (95% CI) lifetime depressive symptoms	13.6 (12.6-14.5)
LR (95% CI) lifetime depressive symptoms	2.7 (2.3-3.2)
PP (95% CI) lifetime (hypo)manic symptoms	17.9 (16.8-19.0)
LR (95% CI) lifetime (hypo)manic symptoms	3.7 (1.9-7.3)

PP= post-test probabilities, LR = likelihood ratio, CI= confidence interval, T_1 = 1 year post-baseline, T_2 = 3 years post-baseline

Post-test probabilities and likelihood ratio bipolar disorder

Table 4.2 lists the PPs and likelihood ratios of lifetime depressive or lifetime manic symptoms for developing a post-baseline bipolar disorder. The PP of developing post-baseline DSM-III-R bipolar disorder given the presence of lifetime (hypo)manic symptoms was 7.1% (4 out of 56), which was considerably higher than the probability of developing bipolar disorder in the group without evidence of subthreshold (hypo)mania (0.2%; 10 out of 4573). The diagnostic overlap expressed as likelihood ratio was 25.4 (95% CI: 10.6-60.6). Similarly, the PP of developing post-baseline bipolar disorder given the presence of lifetime *depressive* symptoms was 1.0% (8 out of 797), which was considerably higher than the probability of developing bipolar disorder in the group without evidence of subthreshold depression (0.2%; 6 out of 3831). The diagnostic overlap expressed as likelihood ratio was 3.3 (95% CI: 2.1-5.3).

Table 4.2 Post-test probabilities and likelihood ratio of lifetime depressive and lifetime (hypo)manic symptoms at baseline for post-baseline bipolar disorder at T_1 or T_2

Lifetime symptoms	Post-baseline bipolar disorder
PP (95% CI) lifetime (hypo)manic symptoms	7.1 (6.4-7.9)
LR (95% CI) lifetime (hypo)manic symptoms	25.4 (10.6-60.6)
PP (95% CI) lifetime depressive symptoms	1.0 (0.7-1.3)
LR (95% CI) lifetime depressive symptoms	3.3 (2.1-5.3)

PP= post-test probabilities, LR = likelihood ratio, CI= confidence interval, T_1 = 1 year post-baseline, T_2 = 3 years post-baseline

Linearity of prediction for lifetime depressive symptoms and post-baseline mood disorders

The PPs and likelihood ratios for increasing level of lifetime depressive symptoms at baseline on developing post-baseline DSM-III-R mood disorder (i.e. major depression or bipolar disorder) are presented in table 4.3. The PP of developing post-baseline mood disorder given the presence of 2 lifetime depressive symptoms was 14.3% (114 out of 797), which was considerably higher than the probability of developing mood disorder without evidence of subthreshold depression (3.9%; 152 out of 3831). The likelihood ratio for this diagnostic overlap was 2.7 (95% CI: 2.3-3.2). In the presence of 7 lifetime depressive symptoms, the PP of developing a post-baseline mood disorder was 22.3% (70 out of 314), which was considerably higher than the probability of developing mood disorder without evidence of subthreshold depression (4.5%; 196 out of 4314). The likelihood ratio was 4.7 (95% CI: 3.7-6.0). In the presence of 23 lifetime depressive symptoms, the PP of developing a post-baseline mood disorder was 50% (2 out of 4), which was considerably higher than the probability of developing mood disorder without evidence of subthreshold depression (5.7%; 264 out of 4624). The likelihood ratio was very high at 16.4 (95% CI: 2.3-116.0). Thus, the PP of developing post-baseline mood disorder increased in a dose-response fashion from 14.3% to 50% and the LR increased from 2.7 to 16.4 from the lowest to the highest number of lifetime depressive symptoms.

Table 4.3 Post-test probabilities and likelihood ratio of increasing levels of lifetime depressive symptoms at baseline for post-baseline mood disorders at T_1 or T_2

No. of lifetime depressive symptoms	No. of respondents with lifetime depressive symptoms	No. of respondents with post-baseline mood disorder	PP (95% CI)	LR (95% CI)
Any	797	114	14.3 (13.3-15.3)	2.7 (2.3-3.2)
2	797	114	14.3 (13.3-15.3)	2.7 (2.3-3.2)
5	542	90	16.6 (15.5-17.7)	3.3 (2.7-4.0)
7	314	70	22.3 (21.1-23.5)	4.7 (3.7-6.0)
9	179	46	25.7 (24.4-27.0)	5.7 (4.2-7.7)
11	100	28	28.0 (26.7-29.3)	6.4 (4.2-9.7)
13	62	20	32.3 (30.9-33.6)	7.8 (4.7-13.1)
15	36	12	33.3 (32.0-34.7)	8.2 (4.2-16.2)
17	19	7	36.8 (35.5-38.2)	9.6 (3.8-24.1)
19	15	5	33.3 (32.0-34.7)	8.2 (2.8-23.8)
21	7	4	57.1 (55.7-58.6)	21.9 (4.9-97.2)
23	4	2	50.0 (48.6-51.4)	16.4 (2.3-116.0)

PP=post-test probabilities, LR = likelihood ratio, CI= confidence interval, T_1 = 1 year post-baseline, T_2 = 3 years post-baseline

Linearity of prediction for lifetime (hypo)manic symptoms and post-baseline mood disorder

As shown in table 4.4 the PP of developing post-baseline mood disorder in presence of 5 lifetime (hypo)manic symptoms was 25% (14 out of 56), which was considerably higher than the probability of developing a mood disorder without evidence of subthreshold mania (5.5%; 252 out of 4573). The likelihood ratio was 5.5 (95% CI: 1.5-20.1). In presence of 7 lifetime (hypo)manic symptoms the PP of developing a post-baseline mood disorder was 50% (2 out of 4), which was considerably higher than the probability of developing a mood disorder without evidence of subthreshold (hypo)mania (5.7%; 264 out of 4625). The likelihood ratio was 16.4 (95% CI: 2.3-116.0). Thus, the PP increased in a dose-response fashion from 25 to 50% and the LR increased from 5.5 to 16.4 from the lowest to the highest number of lifetime (hypo)manic symptoms.

Table 4.4 Post-test probabilities and likelihood ratio of increasing levels of lifetime (hypo)manic symptoms at baseline for post-baseline mood disorders at T_1 or T_2

No. of lifetime (hypo)manic symptoms at baseline	No. of respondents with lifetime (hypo)manic symptoms	No. of respondents with post-baseline mood disorder	PP (95% CI)	LR (95% CI)
Any	56	14	25.0 (23.8-26.3)	5.5 (3.0-9.9)
5	12	3	25.0 (23.8-26.3)	5.5 (1.5-20.1)
7	4	2	50.0 (48.6-51.4)	16.4 (2.3-116.0)

PP= post-test probabilities, LR = likelihood ratio, CI=confidence interval, T_1 = 1 year post-baseline, T_2 = 3 years post-baseline

Discussion

We found a predictive value of lifetime depressive symptoms for post-baseline major depression of 13.6% (95% CI: 12.6-14.5) (LR 2.7; 95% CI: 2.3-3.2) and for post-baseline bipolar disorder of 1.0% (95% CI: 0.7-1.3) (LR 3.3; 95% CI: 2.1-5.3). We determined a predictive value of lifetime (hypo)manic symptoms for post-baseline major depression of 17.9% (95% CI: 16.8-19.0)(LR 3.7; 95% CI: 1.9-7.3) and for post-baseline bipolar disorder of 7.1% (95% CI: 6.4-7.9) (LR 25.4; 95% CI: 10.6-60.6). These results show a high level of cross-prediction across mood symptoms. (Hypo)manic symptoms had higher predictive values and likelihood ratios than unipolar manifestations, not only for bipolar disorder but also for major depression. The higher the number of lifetime mood symptoms of at baseline, the higher the risk for incident mood disorder (major depression or bipolar disorder) during the three years of follow-up, i.e. between baseline and T_2. Predictive values and likelihood ratios ranged from 14.3% to 50% and from 2.7 to 16.4, respectively. Thus, the predictive value of mood symptoms for developing mood disorder increased in a dose-response fashion with increasing numbers of symptoms.

Theoretical implications

The theoretical implications of the findings are that mood symptoms can be seen as intermediary phenotypes of a mood continuum that after exposure to additional risk factors may progress to a full-blown disorder (Hanssen et al., 2003). Additional risk factors may be stressful life events or a positive family history for mood disorders (van Os et al., 2001). Hillegers et al. (2004) showed that, independent of family history, life events increase the risk of a mood disorder in children of patients with bipolar disorder. This is in line with the findings of de Graaf et al. (2002) that negative life events and "ongoing difficulties" are predictors of mood disorders. It has been reported that the personality features characterised by "frequent ups and downs" of mood and the

tendency to experience negative emotions (neuroticism) are risk factors for mood disorders (van Os & Jones, 1999; de Graaf et al., 2002; Angst et al., 2003*b*). Johns and van Os (2001) hypothesised that psychological factors, such as dysfunctional attributions or coping styles, might be important in transition from a subthreshold syndrome to a clinical disorder characterised by need for care.

The higher predictive values of (hypo)manic symptoms than unipolar manifestations, not only for bipolar disorder, but also for major depression suggest that experiencing (hypo)manic symptoms is a stronger indicator of vulnerability for mood disorders and affective dysregulation than depressive symptoms. Cassano et al. (2004) argued that the linear relationship they found between depressive and (hypo)manic symptoms in patients with unipolar and bipolar disorder suggest continuity between these disorders. Unipolar and bipolar disorder can be seen as two extremes of a mood spectrum. The finding in our study of cross-prediction of mood symptoms for developing a mood disorder supports the view of a mood spectrum. Our data are in line with the idea of Angst and Cassano (2005) of a spectrum combining the two dimensional approaches: a continuum from purely depressive symptoms to purely manic symptoms and a continuum of severity.

Screening and prediction

The post-test probability is dependent on the prevalence of the disorder in the studied population (Baldessarini et al., 1983) and increases as the prevalence of the disorder in question rises (Hanssen et al., 2003). The likelihood ratio, on the contrary, is independent of the prevalence of the disorder (Gray, 2004). With exception of the likelihood ratios of (hypo)manic symptoms for bipolar disorder and the likelihood ratios of increasing levels of depressive or (hypo)manic symptoms, the likelihood ratios were relatively low. Although the results suggest that mood symptoms cannot be used readily as a diagnostic/screening tool in the general population for clinical mood disorder it is important for clinicians to monitor people who experience mood symptoms, especially in those cases where additional risk factors are present.

Comparison with previous work

At baseline, the lifetime prevalences of depressive and (hypo)manic symptoms in the absence of either DSM-III-R major depression or bipolar disorder were 17.2% and 1.2%, respectively. Although we used a comparable broad definition of subthreshold (hypo)mania we found a lower rate of subthreshold (hypo)mania compared to the prevalence of up to 8.9% found in other studies (Judd & Akiskal, 2003; Angst et al., 2003*a*). One explanation could be differences in the required duration of symptoms. In the study of Angst et al. (2003*a*), no minimum duration of (hypo)manic symptoms was required. In addition, in the NEMESIS study, only respondents were interviewed

and not their relatives. Hypomanic symptoms and episodes are often experienced as ego-syntonic, while family and significant others generally provide more reliable reports (Akiskal, 2002). Therefore, underreporting of (hypo)manic symptoms can occur in population studies where no information from significant others is collected (Angst et al., 2003*a*).

Limitations

The present study has several limitations. First, a recent reappraisal study of the NEMESIS (Regeer et al., 2004) among respondents with a CIDI diagnosis of bipolar disorder at any of the assessment points, showed that compared to clinical diagnoses made by the Structured Clinical Interview for DSM-IV (SCID, Spitzer et al., 1992) (administered approximately two years later), the CIDI may represent both false positive and false negative results compared to the SCID. Based on the SCID, 40.5% of the respondents with a CIDI diagnosis bipolar disorder and 20 % of the respondents with a CIDI diagnosis major depressive disorder met the criteria for a SCID diagnosis bipolar disorder. Although these findings would seemingly imply that a CIDI diagnosis may not necessarily correspond to a clinical diagnosis of mood disorder, at least part of the discrepancy is likely explained by i) changes in type (unipolar vs. bipolar mood disorder) as well as severity (e.g. subthreshold (hypo)mania vs. syndromal (hypo)mania) of psychopathology occurring between the periods of CIDI and SCID interviews and ii) the use of different polarity weightings in CIDI and SCID rather than a fundamental discordance in diagnosis, as evidenced by the fact that 42 % of the respondents with a CIDI diagnosis of bipolar disorder had a SCID diagnosis of major depressive disorder, so that more than 82.5% of the respondents with a CIDI diagnosis of bipolar disorder still had a major mood disorder diagnosed by the SCID. Therefore, any diagnostic discrepancies between CIDI and SCID would have had little influence on the predictive value and likelihood ratio for lifetime manic or depressive symptoms at baseline for a mood disorder (bipolar disorder or major depression) post-baseline. In addition, the distinction in terms of severity between CIDI symptoms and CIDI diagnosis has face validity, and actually constitutes the main requirement for demonstrating continuity between subthreshold-level and disorder-level mood states, making any comparison with SCID diagnoses less relevant.

Second, although the three-year incidence of bipolar disorder of 0.3% is relatively high in relation to a life-time prevalence of 1.9 %, the number of respondents with lifetime (hypo)manic symptoms and who developed a post-baseline bipolar disorder was rather small, which led to the relative large 95 % confidence interval of the likelihood ratio.

Third, in this study respondents with lifetime psychiatric disorder other than major depression and bipolar disorder were included. In NEMESIS the lifetime

prevalence for at least one DSM-III-R disorder was 41 .2% and 45% of these respondents suffered from more than one disorder (Bijl et al., 1998*b*). Suffering from a psychiatric disorder could predispose for a comorbid mood disorder. However, excluding these respondents would create an unrepresentative sample of "supernormal" individuals with results that cannot be generalised.

Another limitation is that the CIDI does not provide information on the frequency of occurrence of separate symptoms, but only requires information on whether a symptom did or did not occur for a period of at least two weeks for depressive symptoms, or of two days for (hypo)manic symptoms. The possibility that a certain combination of symptoms or their frequent re-occurrence increases the predictive diagnostic value and diagnostic usefulness of subthreshold depression or (hypo)mania could therefore not be ascertained.

Finally, the data were based on retrospective recall. This approach can be problematic in recording lifetime disorders due to difficulties of accurate recall. However, interview techniques such as reading the questions slowly, instructing the respondents to take their time and think carefully before answering, facilitate active memory search. Therefore, the use of intensively trained interviewers, which was the case in NEMESIS, increases accurate reporting of lifetime symptoms (Kessler et al.,1998). In addition, a study of Benazzi and Akiskal (2003) showed that assessment of all non-mood (hypo)manic symptoms, as was done in the CIDI, could help respondents to remember periods of hypomanic behaviour. When the hypomanic behaviour is remembered, respondents often recall a hypomanic mood during the period with hypomanic behaviour.

Conclusions

Depressive symptoms, and to a lesser extent (hypo)manic symptoms, are prevalent in the general population. The present results show a continuum between subthreshold and clinical expression of mood phenotypes over time and a continuum between unipolar and bipolar expression.

In clinical practice, it is important to recognize subthreshold depression and subthreshold mania because these less severe phenotypes of the mood continuum are not only a risk factor for developing a major depressive disorder or bipolar disorder, but they may also lead to psychosocial impairment, decrease of quality of life and high level of mental health care utilisation. Moreover, those subthreshold conditions that are associated with impairment and additional risk factors, such as a positive family history for mood disorders may also benefit from treatment. Further research to identify the factors that contribute to the transition from a subthreshold to a clinical syndrome is likely to clarify the aetiology of mood disorders.

References

Akiskal HS. Classification, diagnosis and boundaries of bipolar disorder. In: Maj M, Akiskal HS, Lopez-Ibor JJ, Satorius N (eds.), Bipolar Disorder, Wiley, London, 2002, pp. 1-52.

Angst J, Merikangas K. The depressive spectrum: diagnostic classification and course. J Affect Disord 1997;45:31-40.

Angst J, Gamma A. A new bipolar spectrum concept: a brief review. Bipolar Disord 2002;4 (Suppl. 1):11-14.

Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rössler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 2003*a*;73:133-146.

Angst J, Gamma A, Endrass J. Risk factors for the bipolar and depression spectra, Acta Psychiatr Scand 2003*b*;108 (Suppl. 418):15-19.

Angst J, Cassano G. The mood spectrum: improving the diagnosis of bipolar disorder. Bipolar Disord 2005;7:4-12.

Baldessarini RJ, Finklestein S, Arana G. The Predictive Power of Diagnostic Tests and the Effect of Prevalence of Illness. Arch Gen Psychiatry 1983;40:569-573.

Benazzi F, Akiskal HS. Refining the evaluation of bipolar II: beyond the strict SCID-CV guidelines for hypomania. J Affect Disord 2003;73:33-38.

Bijl RV, van Zessen G, Ravelli A, de Rijk C, Langendoen Y. The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. Soc Psychiatry Psychiatr Epidemiol 1998*a*;33:581-586.

Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 1998*b*;33:587-595.

Cassano GB, Rucci P, Frank E, Fagiolini A, Dell'Osso L, Shear MK, Kupfer DJ. The Mood Spectrum in Unipolar and Bipolar Disorder: Arguments for a Unitary Approach. American Journal of Psychiatry 2004;161:1264-1269.

Cottler LB, Robins LN, Grant BF, Blaine J, Towle LH, Wittchen HU, Sartorius N. The CIDI-core substance abuse and dependence questions: cross-cultural and nosological issues. The WHO/ ADAMHA Field Trial. British Journal of Psychiatry 1991;159:653-658.

Cuijpers P, Smit F. Subthreshold depression as a risk indicator for major depressive disorder: a systemic review of prospective studies. Acta Psychiatr Scand 2004;109:325-331.

Cuijpers P, de Graaf R, van Dorsselaer S. (2004). Minor depression: risk profiles, functional disability, health care use and risk of developing major depression. J Affect Disord 2004;79:71-79.

Goodwin FK, Ghaemi SN. Understanding Manic-depressive illness. Arch Gen Psychiatry 1998;55:23-25.

Graaf R de, Bijl RV, Smit F, Ravelli A, Vollebergh WA. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Am J Epidemiol 2000;152:1039-47.

Graaf R de, Bijl RV, Ravelli A, Vollebergh WA. Predictors of first incidence of DMS-III-R psychiatric disorders in the general population: findings from the Netherlands Mental Health and Incidence Study. Acta Psychiatr Scand 2002;106:303-313.

Gray GE. Concise guide to evidence-based psychiatry. American Psychiatric Publishing, Arlington, 2004.

Hanssen MSS, Bijl RV, Vollebergh W, van Os J. Self-reported psychotic experiences in the general population: a valid screening tool for DSM-III-R psychotic disorders?. Acta Psychiatr Scand 2003;107:369-377.

Have M ten, Vollebergh WAM, Bijl RV, Nolen WA. Bipolar Disorder in the general population in the Netherlands: results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). J Affect Disord 2002;68:203-213.

Hillegers MHJ, Burger H, Wals M, Reichart CG, Verhulst FC, Nolen WA, Ormel J. Impact of stressful life events, familial loading and their interaction on the onset of mood disorders; study in a high risk cohort of adolescent offspring of parents with bipolar disorder. Br J Psychiatry 2004;185:97-101.

Johns LC, van Os J. The continuity of psychotic experiences in the general population. Clinical Psychology Review 2001;21:1125-1141.

Judd LL, Schettler PJ, Akiskal HS. The prevalence, clinical relevance and public health significance of subthreshold depressions. Psychiatr Clin North Am 2002;25:685-698.

Judd LL, Akiskal SA. The prevalence and disability of bipolar disorder spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. Journal of Affective Disorder 2003;73:123-131.

Kendler KS, Gardner CO. Boundaries of Major Depression: An Evaluation of DMS-IV Criteria. Am J Psychiatry 1998;155:172-177.

Kessler R C, Wittchen HU, Abelson MA, McGonagle K, Schwarz N, Kendler KS, Knäuper B, Zhao S. Methodological studies of the Composite International Diagnostic Interview (CIDI) in the US National Comorbidity Survey (NCS). Int J of Methods in Psychiatr Res 1998;7:33-55.

Krabbendam L, Myin-Germeys I, de Graaf R, Vollebergh W, Nolen WA, Iedema J, van Os J. Dimensions of depression, mania, and psychosis in the general population. Psychol Med 2004;34: 1177-1186.

Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorder during adolescence and young adulthood in a community sample. Bipolar Disord 2000;2:281-293.

Lewinsohn PM, Seeley JR, Klein DN. Bipolar disorder in adolescents: epidemiology and suicidal behaviour. In: Geller B, Del Bello M (eds.), Bipolar disorder in childhood and early adolescence, Guilford Press, New York, 2003, pp 7-24.

Os J van, Park SBG, Jones P-B. Neuroticism, life events and mental health: Evidence for person-environment correlation. Br J Psychiatry 2001;178 (Suppl. 40):s72-s77.

Os J van, Jones P-B. Early risk factors and adult person-environment relationships in affective disorder. Psychol Med 1999;29:1055-1067.

Post R. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 1992;149:999-1010.

Regeer EJ, ten Have M, Rosso ML, Hakkaart-van Roijen L, Vollebergh W, Nolen WA.. Prevalence of bipolar disorder in the general population: a Reappraisal Study of the Netherlands Mental Health Survey and Incidence Study. Acta Psychiatr Scand 2004;110; 374-382.

Robins LN, Wing J., Wittchen HU, Helzer JE, Babor TF, Burke J, Farmer A, Jablenski A,, Pickens R, Regier DA, et al. The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 1988;45:1069-1077.

Sackett DL, Richardson WA, Rosenberg W, Haynes RB. Evidence-based medicine. Churchill Livingstone, New York, 1997.

Semler G, Wittchen HU, Joschke K, Zaudig M, von Geiso T, Kaiser S, von Cranach M, Pfister H.. Test-retest reliability of a standardized psychiatric interview (DIS/CIDI). European Archives of Psychiatry and Neurological Sciences 1987;236:214-222.

Smeets RMW, Dingemans PMAJ, Composite International Diagnostic Interview (CIDI) Version 1.1. World Health Organization: Amsterdam/Geneva, 1993.

Spitzer LR, Williams JBW, Gibbon M, First MW. The Structured Clinical Interview for DSM-II-R (SCID) I: history, rationale, and description. Arch Gen Psychiatry 1992;49:624-629.

StataCorp. STATA Statistical Software: Release 8.0. College Station, Texas, 2002.

Wacker HR, Battegay R, Mullejans R, Schlosser C. Using the CIDI in the general population. In: C. N. Stefanis CN, Rabavilas AD, Soldatos CR (eds.), Psychiatry: a world perspective, Elsevier Science Publishers, Amsterdam, 1990, pp 138-143.

Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. (1991). Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. Br J Psychiatry 1991;159:645-653.

Wittchen HU. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. J of Psychiatr Res 1994;28:57-84.

World Health Organization. Composite International Diagnostic Interview (CIDI), Version 1.0. WHO: Geneva, 1990.

CHAPTER 5

BERKSON'S BIAS AND THE MOOD DIMENSIONS OF BIPOLAR DISORDER

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Abstract

Background

If both depressive and manic episodes independently influence help-seeking behaviour and need for care, a higher level of comorbidity between these dimensions would be found in clinical as compared to non-clinical samples (i.e. Berkson's Bias). The present paper examined whether manic and depressive dimensions independently contribute to mental health service use and determined the degree of comorbidity between manic and depressive dimensions in individuals with and without mental health service use in a general population sample.

Method

Data were derived from the Netherlands Mental Health Survey and Incidence Study (NEMESIS), a prospective epidemiological survey in the Dutch general population. A representative sample of 7076 adults, aged 18-64 years, was interviewed with the Composite International Diagnostic Interview. Dimensions of depression and mania and mental health service use (MHSU) were assessed at baseline, and prospectively 1 and 3 years later. Logistic regression was used to test whether depressive and manic dimensions both had independent effects on mental health service use. The degree of comorbidity between manic and depressive dimensions was assessed as a function of MHSU, both retrospectively and prospectively.

Results

Manic and depressive dimensions contributed independently to mental health service use. Comorbidity of manic and depressive dimensions was significantly higher in respondents with mental health service use than in those without, both retrospectively (16.7% versus 7.1%, P=0.000) and prospectively (10.8% versus 6.6%, P=0.017).

Conclusion

The bipolar phenotype consists of manic and depressive dimensions that may be much more loosely associated than (Berkson) biased clinical observations suggest. Therefore a dimension-specific approach may be more productive in clarifying the aetiology of mood dysregulation.

Key words: bipolar disorder, Berkson's bias, comorbidity, mood dimensions

Introduction

Bipolar disorder is characterised by the occurrence of one or more manic or hypomanic episodes, usually alternating with more or less severe depressive episodes. Several studies have shown that the broad expression of mania and depression occurs at a much higher rate than narrowly defined bipolar disorder, and can also be measured in non-clinical severity at the level of the general population (Angst and Merikangas, 1997; Angst et al., 2003; Cuijpers and Smit, 2004; Cuijpers et al., 2004; Judd et al., 2002; Judd and Akiskal, 2003). Therefore, it can be questioned whether the current concept of bipolar disorder reflects the true nature of mood dysregulation. According to Berkson (1946), high rates of comorbidity seen in clinical practice, such as the apparent cross-sectional or sequential clustering of depressive and manic episodes within the same patient with bipolar disorder, may in part be an artefact if both depressive and manic episodes independently influence help-seeking behaviour and need for care. Since the concept of bipolar disorder is essentially based on observations of help-seeking individuals who have come to the attention of clinicians, the observed association between depressive and manic episodes in these individuals with the most comorbid expressions may rise accordingly, obscuring the fact that depressive and manic dimensional phenotypes may be much more loosely associated with each other in the general population of non-help seeking individuals.

If treatment-seeking bias accounts in part for the high correlation between manic and depressive symptoms in patient populations (Berkson, 1946), correlations should be much lower in the general population than in clinical populations (Maric et al., 2004). This hypothesis was tested, both cross-sectionally and prospectively, in the current paper, by examining whether manic and depressive dimensions independently contribute to mental health service use and determining the degree of comorbidity between manic and depressive dimensions in individuals with and without mental health service use in a general population sample.

Methods

Sample

The Netherlands Mental Health Survey and Incidence Study (NEMESIS) is a prospective study with three assessment points over a period of 3 years (Bijl et al., 1998a; Bijl et al., 1998b). A multistage, stratified, random sampling procedure was used to first select 90 municipalities, then a sample of private households, and finally a Dutch-speaking individual aged 18-64 years within each household. Selected households were sent an introductory letter by the Minister of Health, inviting them to participate. A total of

7076 respondents was interviewed at baseline, representing a response rate of 69.7%. At T_1, one year post-baseline, 5618 respondents participated for the second time; at T_2, 3 years post-baseline, 4848 respondents participated. At T_1 and T_2, the presence of symptoms between respectively baseline and T_1 and between T_1 and T_2 was assessed.

The sample was found to be representative of the Dutch population in terms of gender, marital status and level of urbanisation (Bijl et al., 1998a), with the exception of a slight underrepresentation of individuals in the age group 18-24 years. Examination of attrition suggested that, after adjustment for influences of demographic variables, this had occurred largely independently of the variable of interest: mental health (de Graaf et al., 2000). As this was a study of relative rather than absolute risk, no post-stratification weightings were applied to the data. NEMESIS was conducted with the approval of the Internal Review Board of the Trimbos Institute and after oral explanation of the study, in addition to the introductory letter, all respondents gave informed consent to participate in the study as required by Dutch law at the time of the investigation

Instruments

Respondents were interviewed at home. The Composite International Diagnostic Interview (CIDI) version 1.1 (Robins et al., 1988; Smeets and Dingemans, 1993; WHO, 1990) was used, yielding DSM-III-R diagnoses. The CIDI was designed for trained interviewers who are not clinicians and has been found to have high interrater reliability (Cottler et al., 1991; Wittchen et al., 1991), and high test-retest reliability (Semler et al., 1987; Wacker et al., 1990; Wittchen, 1994). Ninety interviewers experienced in systematic data collection collected the data, having received a 3-day training course in recruiting and interviewing, followed by a 4-day course at the WHO-CIDI training centre in Amsterdam. Extensive monitoring and quality checks took place throughout the entire data collection period (Bijl et al., 1998a).

Assessment of depressive and manic mood symptoms at baseline and follow-up

At baseline, the presence of any lifetime depressive or manic symptom and the total number of lifetime depressive and manic symptoms were assessed with the 28 items of the CIDI depression and dysthymia section (E) and the 11 items of the CIDI mania section (F). All these items can be rated either "yes" (1) or "no" (0). The depressive symptom has to be present for at least 2 weeks and the manic symptom has to be present for at least 2 days. The depression and dysthymia section starts with assessing the presence of depressive mood and/or anhedonia, the mania section starts with assessing the presence of abnormally and persistently elevated, expansive or irritable mood. Secondly, all other associated depressive and (hypo)manic symptoms are assessed. In order to establish a DSM-III-R diagnosis of a mood disorder, the CIDI assesses to what degree

the mood symptoms and the other symptoms were experienced in the same time period. As a result of this procedure, the minimum number of depressive symptoms was two and the minimum number of mania symptoms was three. For the purpose of the analyses, depression and mania were expressed dichotomously as "present" (1) and "absent" (0) in case of two or more lifetime depressive and three or more lifetime manic symptoms, respectively. The lifetime measures of depression and mania at baseline are referred to hereafter as depression-lifetime and mania-lifetime, respectively.

Similarly, a dichotomous variable indicating three or more mania symptoms at baseline and/or T_1 and/or T_2 was constructed (hereafter: mania-total) as well as a similar measure of two or more depression symptoms at baseline and/or T_1 and/or T_2 (hereafter: depression-total). These definitions (depression-lifetime, mania-lifetime, depression-total and mania-total) thus also included the milder forms of minor depression and hypomania.

Mental health service use (MHSU-)

Mental health service use rated at baseline (hereafter: MHSU-lifetime) was defined as a dichotomous variable "yes" (1) or "no" (0). The rating covered lifetime history of mental health service use up to the moment of baseline. Mental health service use was rated "yes" if respondents reported any lifetime contact with: a community mental health centre, a psychiatric outpatient clinic, a private psychiatrist, a psychologist, a psychotherapist, psychiatric admission or day treatment.

In addition, a variable indicating mental health service use at T_1 and/or T_2 was constructed (hereafter: MHSU-follow-up). MHSU-follow-up was scored "yes" if respondents reported receiving mental health service use as defined above for any kind of mental health problems between baseline and T_2.

The risk set for MHSU-follow-up was 4902, consisting of the respondents who had valid data on mental health service use at either T_1 or T_2.

Statistical analysis

Association between mania, depression and MHSU

A logistic regression analysis, yielding odds ratios, was conducted in which MHSU-lifetime was modelled as a function of depression-lifetime and mania-lifetime, entered together, in order to test whether both had independent effects on mental health service use. Similarly, a prospective analysis was also conducted in which MHSU-follow-up was modelled as a function of depression-total and mania-total entered simultaneously in the model, whilst controlling for MHSU-lifetime.

Mania-depression comorbidity rate as a function of MHSU

The degree of comorbidity between mania-lifetime and depression-lifetime was

assessed as a function of MHSU-lifetime, in order to assess the hypothesis that comorbidity would be higher in respondents with a history of help-seeking (i.e. in those with MHSU-lifetime). This was calculated as the difference in the rate of lifetime mania in respondents with depression-lifetime who i) did and ii) did not have MHSU-lifetime, and testing for statistical significance of this risk difference using the MFX procedure in STATA (StataCorp, 2005), which assesses marginal effects and their standards errors after estimation, in this case the STATA LOGISTIC procedure. The same analyses were repeated prospectively using the total measures of symptoms (mania-total and depression-total) and the follow-up of mental health service use (MHSU-follow-up). Thus, the difference in the rate of mania-total in those with presence of depression-total was assessed as a function of first-ever mental health service use occurring between baseline and T_2 (i.e. MHSU-follow-up in those without MHSU-lifetime).

Results

Percentages and number of respondents with mania, depression and MHSU

The mean age of the respondents was 41.2 years, 46.6% were men. The percentages and number of respondents with depression-lifetime, mania-lifetime, depression and mania-lifetime, depression-total, mania-total, depression and mania-total, MHSU-lifetime and MHSU-follow-up, are presented in table 5.1.

Table 5.1 Percentages and number of respondents with depression, mania and mental health service use (MHSU) (N=7076)

	% (N)
Depression-lifetime	31.5 (2225)
Mania-lifetime	4.1 (293)
Mania + depression-lifetime	3.52 (249)
Depression-total	36.5 (2585)
Mania-total	5.0 (356)
Mania + depression-total	4.4 (311)
MHSU-lifetime	19.1 (1352)
MHSU-follow-up $	21.7 (1065)

$ N=4902

Association between mania, depression and MHSU

Table 5.2 presents the association between mania and depression on the one hand and MHSU on the other expressed as odds ratios (OR). Depression-lifetime was strongly associated with MHSU-lifetime (OR 7.6; 95% CI: 6.7-8.7), and so was mania-lifetime (OR 2.6; 95% CI: 2.0-3.4), albeit with a lower effect size. For MHSU-follow-up similar associations were found with mania-total and depression-total. Both depression-total (OR 9.3; 95% CI: 7.9-11.0) and mania-total (OR 2.8; 95% CI: 2.1-3.8) were significantly associated with MSHU-follow-up. These associations remained significant when controlling for MSHU-lifetime indicating that the prospective (follow-up) associations were not merely repetitions of previous mental health service use.

Table 5.2 Association between mania and depression on the one hand, entered together in the model, and mental health service use (MHSU) on the other expressed as odds ratio (95% CI)

	Mania-lifetime	**Depression-lifetime**
MHSU-lifetime (95% CI)	2.6 (2.0-3.4)*	7.6 (6.7-8.7)*
	Mania-total	**Depression-total**
MHSU-follow-up (95% CI) $	2.8 (2.1-3.8)*	9.3 (7.9-11.0)*
MHSU-follow-up (95% CI) $ corrected for MHSU-lifetime	2.5 (1.9-3.4)*	7.5 (6.3-9.0)*

** P=0.000, $ N=4902*

Mania-depression comorbidity rate as a function of MHSU

Table 5.3 shows the degree of comorbidity between mania and depression in respondents with and without MHSU. In respondents with MHSU-lifetime, the rate of mania-lifetime given the presence of depression-lifetime was 16.7%, which was considerably higher than the rate among respondents without MHSU-lifetime (7.1%). The comorbidity difference of 9.6% (95% CI: 6.8%-12.3%) for mania-lifetime given the presence of depression-lifetime between respondents with and without MHSU-lifetime, was highly significant (z=6.82, *P*=0.000). In respondents with first-ever mental health service use (i.e. MHSU-follow-up in those without MHSU-lifetime) the rate of mania-total given the presence of depression-total was 10.8%, which was considerably higher than the rate of mania-total given the presence of depression-total among respondents without MHSU-follow-up (6.6%). The comorbidity difference of 4.2% (95% CI: 0.8%-7.7%) for mania-total given the presence of depression-total between respondents with and without MHSU-follow-up, was again significant (z=2.39, *P*=0.017).

Table 5.3 Mania-depression comorbidity rate (%) and comorbidity differences (%) as a function of mental health service use (MHSU)

	MHSU-lifetime	**No MHSU-lifetime**	**Comorbidity difference (95% CI)**
Mania-depression lifetime comorbidity rate (risk set: N=2225) $	16.7	7.1	9.6 (6.8-12.3)*
	MHSU-follow-up	**No MHSU-follow-up**	**Comorbidity difference (95% CI)**
Mania-depression total comorbidity rate (risk set: N=1143) $$	10.8	6.6	4.2 (0.8-7.7)**

**P=0.000, **P=0.017, $ Risk set of 2225 respondents with depression-lifetime,*
$$ Risk set of 1143 respondents with depression-total and without MHSU-lifetime

Discussion

This study examined the association between manic and depressive dimensions and mental health service use, and the degree of comorbidity between manic and depressive dimensional phenotypes in individuals with and without mental health service use in a general population sample. The odd ratios we found illustrate that both manic and depressive dimensions contributed independently to retrospective and prospective mental health service use. As a result, comorbidity of manic and depressive dimensions was significantly higher in individuals with mental health service use, both retrospectively and prospectively in contrast to individuals without mental health service use.

These results, therefore, suggest that the current concept of bipolar disorder is in part the result of Berkson's bias. The association between both dimensions in clinical samples appears to be high due to the fact that both manic and depressive dimensions contribute to help-seeking behaviour and need for care. These independent effects of both dimensions on help-seeking will lead to an increase in the number of patients in clinical samples with manic-depression comorbidity. Consequently, manic and depressive dimensions are much more loosely associated with each other in the general population of non-help seeking individuals. Recent evidence suggesting that the bipolar phenotype is continuous in the general population (Angst and Merikangas, 1997; Angst et al., 2003; Cuijpers and Smit, 2004; Cuijpers et al., 2004; Judd et al., 2002; Judd and Akiskal, 2003; Regeer et al., 2006) taken together with the current results, strongly support a dimensional rather than a categorical approach of the bipolar phenotype in which an individual can have more or less psychopathology rated on several dimensions such as severity and polarity of mood dysregulation.

The theoretical implications of the findings are that it may be rewarding in the search for the aetiology of bipolar disorder to look for separate risk factors for manic and for depressive dimensions. This is in line with the two-illness model of bipolar disorder proposed by Joffe et al. (1999). These authors hypothesised that bipolar disorder constitutes two separate but related disorders, depression and mania. This hypothesis has face validity given the fact that bipolar depression is no different from unipolar depression. Although criticized (Bowden, 1999; Dunner, 1999; Swann, 1999) the model is theoretically interesting to re-evaluate the concept of bipolar disorder because research to date has not provided a clear picture of the aetiology of mood dysregulation. The relatively independent variation identified in the present study reflects the fact that mania and depression are syndromes not specific to bipolar disorder but also arise in a variety of neuromedical and toxicological conditions (Baldessarini, 2000; Swann, 1999). Among the latter groups is mania during the use of corticosteroids, withdrawal or abuse of drugs and encephalitis (Krauthammer and Klerman, 1978) and depression as a comorbid disorder in other psychiatric disorders, chronic somatic conditions (Schweitzer et al., 2005), or as a result of the use or withdrawal of drugs or medication. Therefore, mania and depression may be better seen as syndromes with at least partial different aetiologies and underlying pathophysiologies (Kelsoe, 2003). More recently, Schweitzer et al. (2005) argued that bipolar disorder is more appropriately viewed as a manic disorder with or without comorbid depression because the syndrome of mania is the central distinguishing feature of bipolar disorder. Most psychiatric disorders are commonly complicated by co-morbid depression. Depression in bipolar disorder has been viewed as an integral part of the disorder, whereas in other psychiatric disorders depression has been viewed as a complicating and co-existing comorbid disorder.

The observation of relatively separate manic and depressive dimensions in the general population contrasts with the phenomenon of mixed episodes seen in clinical samples. The co-occurrence of manic and depressive symptoms in the same mood episode is common in clinical practice. A recent study among 441 treated individuals with bipolar disorder showed occurrence of clinically significant depressive symptoms (two or more symptoms) in 94.1 % of those with a (hypo)mania; similarly, 70.1% of those in a depressive state episode had clinically significant manic symptoms (Bauer et al., 2005). In addition, another study with 908 treated individuals found that in over 57% hypomania co-occurs with depression (Suppes et al., 2005). The present study suggests that these observations may be influenced by Berkson's Bias.

Probably many different genes contribute to the aetiology of most if not all major psychiatric syndromes (Kendell & Jablensky, 2003). Some syndromes and symptom dimensions may share the same genes and some genes may be specific for a symptom dimension (Cardno et al., 2001; Kendell & Jablensky, 2003). For example, the same regions on chromosome 13 and 22 are linked with psychotic symptoms

during affective episodes and schizophrenia (MacQueen et al., 2005). A recent study by Williams et al. (2006) suggests that variation at the DAOA/G30 locus on chromosome 13 influences susceptibility to major mood episodes (depression and mania) in individuals with schizophrenia and in individuals with bipolar disorder. Another study investigated the involvement of variations at the Brain-Derived Neurotrophic Factor (BDNF) gene locus in major depressive disorder, bipolar disorder and schizophrenia. The results of this study suggest that BDNF may be a susceptibility gene for major depressive disorder and schizophrenia with lifetime depressive symptoms (Schumacher et al., 2005). Variations in the genes DISC1 and neuregulin 1 (NRG1) may confer susceptibility to a form of illness with mixed features of psychosis and mania (Craddock et al., 2006). These studies support the possibility of relatively specific relationships between genotype and symptom-dimensions.

In addition, a dimensional approach may also contribute to improvements in the treatment of mood disorders by focussing more on dimension-specific treatments, as indeed appears to be becoming more the case.

Limitations

The data were based on retrospective recall. This approach can be problematic in recording lifetime symptoms and disorders due to difficulties of accurate recall. However, interview techniques such as reading the questions slowly, instructing the respondents to take their time and think carefully before answering, facilitate active memory search. Therefore, the use of intensively trained interviewers, which was the case in NEMESIS, increases accurate reporting of lifetime symptoms (Kessler et al., 1998).

A recent reappraisal study of the NEMESIS (Regeer et al., 2004) among respondents with a CIDI diagnosis of bipolar disorder at any of the assessment points, showed that compared to clinical diagnoses made by the SCID (administered approximately two years later), the CIDI may represent both false positive and false negative results compared to the SCID. However, the reappraisal study assessed clinical diagnosis and was not designed to assess at the level of symptoms. Therefore, the presents results based on symptom dimensions has face validity. The CIDI assessment of mood symptoms does not include the degree of distress or disability associated with symptoms. Therefore the CIDI probably yields higher prevalence rates of manic and depressive symptoms than an instrument, which requires that each symptom must be distressing (Krabbendam et al., 2004). However, these milder expressions of depressive or manic symptoms determined by the CIDI should not be seen as false positive, as there is evidence that these less severe phenotypes of mood disorder are a risk factor for developing a major depressive disorder or bipolar disorder (Regeer et al., 2006).

Another limitation is that mixed episodes were not assessed by the CIDI in the present sample of the general population. Therefore the influence of Berkson's bias on the clinical concept of mixed episodes was not tested.

References

Angst J, Merikangas K. The depressive spectrum: diagnostic classification and course. J Affect Disord 1997;45:31-40.

Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rössler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 2003;73:133-146.

Baldessarini RJ. A plea for integrity of the bipolar disorder concept. Bipolar Disord 2000;2:3-7.

Bauer MS, Simon GE, Ludman E, Unützer J. 'Bipolarity' in bipolar disorder: distribution of manic and depressive symptoms in a treated population. Br J Psychiatry 2005;187:87-88.

Berkson J. Limitations of the application of the fourfold table analysis to hospital data. Biometrics 1946;2:47–53.

Bijl RV, van Zessen G, Ravelli A, de Rijk C, Langendoen Y. The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. Soc Psychiatry Psychiatr Epidemiol 1998*a*;33:581-586.

Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 1998*b*;33:587-595.

Bowden CL. "A two-illness model of bipolar disorder" – by RT Joffe, LT Young, GM MacQueen: a commentary. Bipolar Disord 1999;1:31-35.

Cardno AG, Sham PC, Murray RM, McGuffin P. Twin study of symptom dimensions in psychoses. Br J Psychiatry 2001;179:39-45.

Cottler LB, Robins LN, Grant BF, Blaine J, Towle LH, Wittchen HU, Sartorius N. The CIDI-core substance abuse and dependence questions: cross-cultural and nosological issues. The WHO/ ADAMHA Field Trial. Br J Psychiatry 1991;159:653-658.

Craddock N, O'Donovan MC, Owen MJ. Genes for Schizophrenia and Bipolar Disorder? Implications for Psychiatric Nosology. Schizophr Bull 2006;32:9-16.

Cuijpers P, Smit F. Subthreshold depression as a risk indicator for major depressive disorder: a systemic review of prospective studies. Acta Psychiatr Scand 2004;109:325-331.

Cuijpers P, de Graaf R, van Dorsselaer S. Minor depression: risk profiles, functional disability, health care use and risk of developing major depression. J Affect Disord 2004;79:71-79.

Dunner DL. "A two-illness model of bipolar disorder" – by RT Joffe, LT Young, GM MacQueen: a commentary. Bipolar Disord 1999;1:31-35.

de Graaf R, Bijl RV, Smit F, Ravelli A, Vollebergh WA. Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Am J Epidemiol 2000;152:1039-1047.

Joffe TR, Young LT, MacQueen GM. A two-illness model of bipolar disorder. Bipolar Disord 1999;1:25-30.

Judd LL, Schettler PJ, Akiskal HS. The prevalence, clinical relevance and public health significance of subthreshold depressions. Psychiatr Clin North Am 2002;25:685-698.

Judd LL, Akiskal SA. The prevalence and disability of bipolar disorder spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. J Affect Disord 2003;73:123-131.

Kelsoe JR . Review: Arguments for the genetics basis of the bipolar spectrum. J Affect Disord 2003;73:183-197.

Kendell R, Jablensky A. Distinguishing Between the Validity and Utility of Psychiatric Diagnoses. Am J Psychiatry 2003;160: 4-12.

Kessler R C, Wittchen HU, Abelson MA, McGonagle K, Schwarz N, Kendler KS, Knäuper B, Zhao S. Methodological studies of the Composite International Diagnostic Interview (CIDI) in the US National Comorbidity Survey (NCS). Int J of Methods in Psychiatr Res 1998;7:33-55.

Krabbendam L, Myin-Germeys I, de Graaf R, Vollebergh W, Nolen WA, van Os J. Dimensions of depression, mania, and psychosis in the general population. Psychol Med 2004;34:1177-1186.

Krauthammer C, Klerman GL. Secondary mania: manic syndromes associated with antecedent physical illness or drugs. Arch Gen Psychiatry 1978;35:1333-1339.

Maric N, Myin-Germeys I, Delespaul P, de Graaf R, Vollebergh W, van Os J. Is our concept of schizophrenia influenced by Berkson's bias?. Soc Psychiatry Psychiatr Epidemiol 2004;39:600-605.

MacQueen GM, Hajek T, Alda M. The phenotypes of bipolar disorder: relevance for genetic investigations. Mol Psychiatry 2005;10:811-826.

Regeer EJ, ten Have M, Rosso ML, Hakkaart-van Roijen L, Vollebergh W, Nolen WA. Prevalence of bipolar disorder in the general population: a Reappraisal Study of the Netherlands Mental Health Survey and Incidence Study. Acta Psychiatr Scand 2004;110:374-382.

Regeer EJ, Krabbendam L, de Graaf R, ten Have M, Nolen WA, van Os J. A prospective study of the transition rates of subthreshold (hypo)mania and depression in the general population. Psychol Med 2006;36:619-628.

Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, Farmer A, Jablenski A, Pickens R, Regier DA, et al. The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 1988;45:1069-1077.

Schumacher J, Jamra RA, Becker T, Ohlraun S, Klopp N, Binder EB, Schulze TG, Deschner M, Schmäl C, Höfels S, Zobel A, Illig T, Propping P, Holsboer F, Rietschel M, Nother MM, Cichon S. Evidence for a Relationship Between Genetic Variants at the Brain-Derived Neurotrophic Factor (BDNF) Locus and Major Depression. Biol Psychiatry 2005;58:307-314.

Schweitzer I, Maguire K, Hg CH. Should bipolar disorder be viewed as manic disorder? Implications for bipolar depression. Bipolar Disord 2005;7:418-423.

Semler G, Wittchen HU, Joschke K, Zaudig M, von Geiso T, Kaiser S, von Cranach M, Pfister H. Test-retest reliability of a standardized psychiatric interview (DIS/CIDI). Eur Arch Psychiatry Neurol Sci 1987;236:214-222.

Smeets RMW, Dingemans PMA. Composite International Diagnostic Interview (CIDI) Version 1.1. World Health Organization, Amsterdam Geneva, 1993.
StataCorp. STATA Statistical Software: Release 9.0. College Station, Texas, 2005.

Suppes T, Mintz J, McElroy SL, Altshuler LL, Kupka RW, Frye MA, Keck PE Jr, Nolen WA, Leverich GS, Grunze H, Rush AJ, Post RM. Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Foundation Bipolar Treatment Network: a sex-specific phenomenon. Arch Gen Psychiatry 2005;62:1089-1096.

Swann AC. "A two-illness model of bipolar disorder" – by RT Joffe, LT Young, GM MacQueen: a commentary. Bipolar Disord 1999;1:31-35.

Wacker HR, Battegay R, Mullejans R, Schlosser C. Using the CIDI in the general population. In: Stefanis CN, Rabavilas AD, Soldatos CR (eds.), Psychiatry: a world perspective, Elsevier Science Publishers, Amsterdam, 1990.

Williams NM, Green EK, Macgregor S, Dwyer S, Norton N, Williams H, Raybould R, Grozeva D, Hamshere M, Zammit S, Jones L, Cardno A, Kirov G, Jones I, O'Donovan MC, Owen MJ, Craddock N. Variation at the DAOA/G30 Locus Influences Susceptibility to Major Mood Episodes but Not Psychosis in Schizophrenia and Bipolar Disorder. Arch Gen Psychiatry 2006;63:366-373.

Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. Br J Psychiatry 1991;159:645-653.

Wittchen HU. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. J Psychiatr Res 1994;28:57-84.

World Health Organization. Composite International Diagnostic Interview (CIDI), Version 1.0. Geneva, 1990.

CHAPTER 6

RECOGNITION AND TREATMENT OF BIPOLAR DISORDER IN THE GENERAL POPULATION

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Abstract

Objectives

In the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (N=7076), a high rate of underdiagnosis (54%) and undertreatment (85%) was found among the 136 respondents who where diagnosed by the Composite International Diagnostic Interview (CIDI) with a bipolar disorder. The aim of this study was to identify factors that may explain these high rates and to determine the consequences in terms of costs.

Methods

In a reappraisal study of NEMESIS we identified 40 respondents with bipolar disorder confirmed by the Structured Clinical Interview for DSM-IV (SCID). Data on illness characteristics, treatment history, subjective opinions of their diagnosis and cost were collected.

Results

The majority of the respondents consulted their general practitioner (N=36, 90%) and mental health care (N=25, 62.5%) for their problems. Only five respondents (12.5%) were diagnosed with bipolar disorder, did agree with this diagnosis, and used a mood stabilizer. Ten (25%) respondents thought they had a depressive disorder, 18 (45%) another disorder and 7 (17.5%) respondents were convinced that they had no disorder. Over 70% (N=10) of the respondents with a bipolar I disorder and over 90% (N=13) with a bipolar II disorder were not diagnosed or disagreed with the diagnosis. No significant differences in number of mood episodes, comorbidity and costs were found between respondents with a recognized and unrecognized bipolar disorder.

Conclusions

Self-recognition of bipolar disorder is an important factor in treatment seeking and receiving adequate treatment. Type of bipolar disorder, number of mood episodes, and comorbidity did not influence recognition.

Key words: bipolar disorder, recognition, treatment, general population

Introduction

Bipolar disorder is a lifelong recurrent illness that can have serious consequences such as poor social and occupational functioning, impaired quality of life (Calabrese et al., 2003; Hakkaart-van Roijen et al., 2004; Morselli et al., 2004), a high rate of suicide (Goodwin & Jamison, 2007; Dunner 2003) and risky behaviour that is destructive to the patient and their relatives (Hirschfeld, 2001). Population-based (Regier et al., 1993; Kessler et al., 1997; ten Have et al., 2002; Hirschfeld et al., 2003*a*; Wang et al., 2005; Schaffer et al., 2006;) and clinical-based studies (Manning et al., 1997; Hantouche et al., 1998; Ghaemi et al., 1999; Ghaemi et al., 2000; Das et al., 2005; Hirschfeld et al., 2005; Mantere et al., 2004) in general practice and mental health settings report that bipolar disorder is underdiagnosed and undertreated. Retrospective studies among patients with bipolar disorder report long delays between onset of first symptoms or the first (hypo)manic episodes and receiving the correct diagnosis or start of treatment (Lish et al., 1994; Suppes et al., 2001; Hirschfeld et al., 2003*b*; Morselli et al., 2003). The most common inaccurate diagnosis is major depressive disorder (Ghaemi et al., 2000, Lish et al., 1994, Hirschfeld et al., 2003*b*). Misdiagnosis may lead to inappropriate treatment, such as prescription of antidepressant without a mood stabilizer with the risk of less efficacy (Sachs et al., 2000; Ghaemi et al., 2001) and the induction of (hypo)mania or a rapid cycling course (Hirschfeld, 2001; Altshuler et al., 1995).

Goldberg and Huxley have suggested a model for understanding the pathway by which individuals become defined as mentally ill and eventually reach mental health care (Goldberg & Huxley, 1980; Goldberg & Huxley 1992). The model consisted of five levels, each one corresponding to a different point on the pathway to psychiatric care. Four filters were postulated between these five levels. The first filter is the decision of people in the community (level one) to seek help for their problems and consult their general practitioner (level two). The second filter is the general practitioner to detect a psychiatric disorder (level three). The third filter is the decision to refer to specialized mental health care (level four). The fourth filter is the decision to hospitalize a patient in a psychiatric hospital (level five).

On the level of the community large population studies are done on the epidemiology of mental illness. Percentages of respondents with a 12-month bipolar disorder who received treatment in mental health care facilities the year prior to the interview were found ranging from 20% in the National Comorbidity Survey (NCS, Kessler et al., 1997) and 33.8% in the National Comorbidity Survey Replication (NCS-R, Wang et al., 2005) to 59% in the Epidemiologic Catchment Area study (ECA, Regier et al., 1993). Also in the Netherlands Mental Health Survey and Incidence Study (NEMESIS) a high rate of underdiagnosis and undertreatment was found (Bijl et al., 1998*a*; Bijl et al., 1998*b*). As in the NCS, this general population study used the Composite International

Diagnostic Interview (CIDI), a fully structured interview administered by lay interviewers. Among the 7076 respondents in NEMESIS 136 were diagnosed with bipolar disorder according to DSM-III-R. Fifty-nine of them (43%) reported that they had never sought help from mental health care, and another 14 (10%) that they never had discussed their manic episode, indicating that at least 73 (54%) never had been diagnosed as such. In addition, only 38 (28%) had received mental health system care (MHS-care) during the past year, while only 18 (13%) reported that they had used medication, indicating an even higher rate of undertreatment of around 85% (ten Have et al., 2002).

Indications for underdiagnosis of bipolar disorder were also found in another population study (Hirschfeld et al., 2003*a*). In this study 85.358 subjects completed the Mood Disorders Questionnaire (MDQ). The adjusted positive screen rate for bipolar I or II disorder was 3.7%. Only 20 % of the individuals with a positive screen reported that they had previously received a diagnosis of bipolar disorder from a physician, 31% had received a diagnosis of unipolar depression, and 49% had received neither of these diagnoses.

Studies performed in general practice also show underdiagnosis of bipolar disorder. In a sample of 108 patients initially diagnosed with a depressive disorder, 26% were diagnosed with bipolar disorder or cyclothymia when re-examined by trained family physicians with the SCID (Manning et al., 1997). In another study among 649 patients treated in general practice for depression with antidepressants, 21% screened positive for bipolar disorder on the MDQ of whom 67% reported never been diagnosed as such (Hirschfeld et al., 2005).

Studies at the level of mental health care settings also indicate that recognition of bipolar disorder is poor. In a recent Finish study 191 (12%) of 1630 non-schizophrenic in- and outpatients treated in psychiatric settings were diagnosed by the SCID with a bipolar I or II disorder; 26% of the bipolar I disorder patients and 51% of the bipolar II disorder patients were previously undiagnosed (Manterre et al., 2004). In a French study of 250 in- and outpatients presenting with a depressive episode, 40% were diagnosed with bipolar II disorder. Only half of these respondents were known with bipolar disorder to the clinicians at entry of the study (Hantouche et al., 1998).

These studies about recognition of bipolar disorder were performed at different levels of the filter model. At the level of the general population, epidemiological studies were performed by trained lay interviewers with fully structured interviews (CIDI) asking only globally about diagnostic and treatment issues, e.g. whether the respondent ever had contacted a medical doctor or mental health specialist (Wittchen 2004) or whether they had mentioned (hypo)manic symptoms to a medical doctor or mental health care professional (ten Have et al., 2002). In the surveys by Hirschfeld et al. (2003*a*) in the general population and in general practice (Hirschfeld et al., 2005) a screening instrument, the MDO, that has good specificity but relative low sensitivity especially

for bipolar II/NOS disorders (Hirschfeld et al., 2003c; Miller et al., 2004; Weber Rouget et al., 2005) was used and recognition was based on self-report not confirmed by illness history from professionals. At the level of general practice the study of Manning et al. (1997) used a semi-structured clinical instrument (SCID) in patients who sought help for depression. At the level of mental health care, studies used clinical instruments (such as the SCID) to make diagnoses while recognition was based on former diagnosis of professionals.

We are not aware of any study examining recognition and treatment patterns in which respondents were recruited from the general population (and therefore did not pass any filter of the Goldberg Huxley model) and were interviewed by clinicians with a clinical interview. Moreover, it remains unclear from the above mentioned studies, which factors can explain the high rates of underdetection and undertreatment. In addition, little is known about the consequences of underrecognition and undertreatment. In the present study we attempt to address these issues.

Recently, we performed a reappraisal study among all NEMESIS respondents with bipolar disorder (Regeer et al., 2004). In that study we re-interviewed 74 respondents with a CIDI/DSM-III-R bipolar disorder and also 40 respondents with CIDI/DSM-III-R major depressive disorder who had participated in all three interviews of NEMESIS, with the Structured Clinical Interview for DSM-IV (SCID), a semi-structured interview performed by clinicians (Spitzer et al., 1992). Thus, we identified 40 respondents with a SCID/DSM-IV diagnosis of bipolar disorder (Regeer et al., 2004).

In the present study we examined the degree of recognition and treatment of bipolar disorder in this sample, identified factors influencing recognition and treatment, and determined the direct and indirect costs of these disorders. We hypothesized a priori that self-recognition of bipolar disorder is important for treatment seeking and that especially respondents with less severe types of bipolar disorder (bipolar disorder NOS and cyclothymia) would not recognize having an illness; that respondents with bipolar II disorder who are expected to suffer mostly from their depressive episodes would not consult a health professional for hypomanic episodes; and that a higher number of (hypo)manic episodes would improve recognition. We also hypothesized that underdiagnosis and undertreatment would be partly explained by the presence of comorbid disorders that may complicate the diagnosis of bipolar disorder. In addition, we examined whether underdiagnosis and undertreatment of bipolar disorder would lead to higher indirect costs due to impaired functioning, while direct cost were expected to be the highest for respondents with recognized bipolar disorder.

Materials and methods

Study sample

Respondents were selected from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) sample. NEMESIS is a prospective study in the Dutch general population (N = 7076) aged 18 to 64, with three assessment points (baseline, T_1 and T_2) in 1996, 1997 and 1999. The respondents accurately reflected the Dutch population in terms of gender, civil status, and urbanicity, with the exception of a slight underrepresentation of individuals in the age group between 18 and 24 years (Bijl et al., 1998*a*, Bijl et al., 1998*b*). In this paper we focus on those 40 respondents who fulfilled the SCID/DSM-IV criteria for a bipolar disorder in the reappraisal study as described above. The response rate in the reappraisal study was moderate. Of all 158 respondents who were identified with a lifetime bipolar disorder at any of the three assessment points in NEMESIS 105 indicated that they could be contacted in case of follow-up studies. Ultimately 74 respondents participated in the reappraisal study, i.e. 46.8% of the total sample with a bipolar disorder. The participants (N=74) were significantly older, higher educated and more employed than the non-participants (N=84). There were no significant differences regarding gender, household composition, urbanicity, income, comorbidity and prevalence of bipolar I disorder versus bipolar disorder NOS. In order to keep the interviewers blind for the original CIDI/DSM-III-R diagnosis a second group of 57 respondents with a lifetime diagnosis of major depressive disorder was selected of whom 40 (70%) participated in the study. No significant differences between participants and non-participants were found regarding sociodemographic factors and comorbidity. All respondents were interviewed at home between August 2001 and February 2002. The Medical Ethical Review Board of the University Medical Center Utrecht approved the study. Written informed consent was obtained from all respondents.

Diagnosis and recognition

All respondents were assessed with the SCID for their current and lifetime DSM-IV diagnosis. In addition they were asked about their own opinion of their diagnosis with the following questions: "What do you think you are/were suffering from?" and "What diagnosis did you receive when seeking help for your mood problems?" (see Appendix A). Bipolar disorder was recognized if the respondents indicated suffering from bipolar disorder and having received the diagnosis when consulting a health professional.

Illness characteristics and comorbidity

Type of bipolar disorder and comorbid DSM-IV diagnoses, as well as age at first depressive and first (hypo)manic episode and number of overall mood, depressive

and (hypo)manic episodes were assessed with the SCID. To reduce the influence of respondents who experienced very high numbers of depressive and (hypo)manic episodes the median was used to describe the number of overall mood, (hypo)manic and depressive episodes. Onset of bipolar disorder was explored by questions about age at first symptoms, type of first symptoms and type of first mood episode.

Help seeking behaviour and treatment history

The treatment history was examined using a questionnaire covering the following topics; consultation of health professionals, reasons for not seeking help, recognition of the disorder by the respondent and health professionals, and received treatment (see Appendix A). Respondents were considered to have received adequate treatment for bipolar disorder when they had ever used a mood stabilizer (lithium, carbamazepine or valproate) and had frequent contact with a psychiatrist or psychologist.

Direct and indirect costs

The 'Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness' (TiC-P) (Hakkaart-van Roijen, 2002) was used to collect data on direct and indirect costs generated by bipolar disorder. Direct costs were defined as costs due to medical consumption in the 4 weeks preceding the interview and were assessed by questions on the number of contacts with a general practitioner (GP), psychiatrist, medical specialists (that is, medical professionals working at a hospital), physiotherapist, alternative health practitioners, the day care/hospital length of stay, and the use of medication. The yearly costs were calculated from the medical consumption 4 weeks prior tot the interview. The indirect costs were defined as the productivity loss due to absence from work and reduced efficiency at work. To collect data on productivity loss, respondents with paying jobs (N=30) were asked to indicate the number of days they had been absent from work and to estimate the number of extra hours they should have worked to compensate for productivity loss due to health-related problems in the 2 weeks preceding the interview (Hakkaart-van Roijen et al., 2004).

Statistics

Analyses were carried out with SPSS 11.0 for Windows. We used summary statistics to describe the sample. Data were analyzed using standard cross tabulation. Chi-Square test and Fischer exact test of significance were used to compare percentages of respondents who consulted a health professional, used medication and received psychological treatment between groups. One-way Anova procedures were used to compare continuous variables (such as age at consultation of general practitioner and mental health care, direct and indirect cost, number of comorbid disorder) between groups. To compare the median number of (hypo)manic, depressive and total episodes

between the different groups the Kruskal-Wallis and Mann-Whitney U test was used. A significance level of $P < 0.05$ was used.

Results

Diagnosis and recognition (table 6.1)

The sample consisted of 14 respondents with bipolar I disorder, 14 with bipolar II disorder (including one who developed a manic episode during the use of an antidepressant), 7 with bipolar disorder NOS, 3 with cyclothymia and 2 with a bipolar disorder substance (antidepressant) induced. For the analyses the latter three groups are taken together as other bipolar disorder.

Regarding their own idea about the diagnosis, 5 of the 40 (12.5%) respondents were diagnosed with bipolar disorder by a mental health care professional and did agree with the diagnosis. This concerned 4 of 14 (28.6%) with bipolar I disorder, 1 of 14 (8.3%) with bipolar II disorder and none of the respondents with a diagnosis other bipolar disorder (NS). Ten respondents thought they were suffering from a depressive disorder. Of the 18 respondents with other own diagnoses, 8 answered that they had suffered from "burn out", and the other 10 had received the following diagnoses: psychosis; psychosis post partum; psychosis, depression and borderline personality disorder; anxiety disorder (2 respondents); bulimia and anxiety disorder; cluster A personality disorder and development disorder; "emotional neglect"; posttraumatic stress disorder; and adjustment disorder after discovery of cancer. Seven respondents had not received or did not report any diagnosis.

Illness characteristics and comorbidity (table 6.1)

No significant differences were found in age of onset of (hypo)manic episode and duration since start of symptoms until first mood or first (hypo)manic episode between the subgroups of SCID diagnoses or between the subgroups of own diagnoses.

In 34 respondents we could determine whether their illness had started with a depressive episode or a (hypo)manic episode. In 3 of 4 respondents with other bipolar disorder who never had a full hypomanic episode, there was information whether their illness had started with depressive symptoms or (hypo)manic symptoms. For the analysis we grouped these 37 respondents together. In 18 respondents (48.6%) their illness started with a depressive episode or depressive symptoms at a mean age of 23.9 years (median 20.5 years). In 9 respondents (24.3%) the bipolar disorder started with a (hypo)manic episode or (hypo)manic symptoms at a mean age of 30.3 years (median 35 years). Ten respondents (27%) experienced the first depressive episode and the first (hypo)manic episode in the same year at a mean age of 25.4 years (median 22

years). There were no differences in whether the illness had started with a depressive episode between the subgroups of SCID diagnoses or own diagnoses.

Eight respondents with other bipolar disorder (N=4) and bipolar II disorder (N=4) had histories of very high numbers of depressive and hypomanic episodes. In five respondents the number of episodes was unknown: in one respondent with bipolar I disorder and in four respondents with other bipolar disorder the number of episodes was not assessable (see legend table 6.1). Taken this missing information into account, there were no differences in the median number of all mood episodes and the median number of depressive episodes between the subgroups of SCID diagnoses or own diagnoses. There was however a significant difference in number of (hypo)manic episodes between the subgroups of SCID diagnosis (P=0.049), but contrary to our hypothesis, not between the subgroups of own diagnosis. The number of (hypo)manic episodes was significantly higher in respondents with bipolar II disorder in comparison to bipolar I disorder (P=0.005).

Regarding comorbidity, no differences were found in number of comorbid SCID diagnoses between respondents with bipolar I disorder, bipolar II disorder and other bipolar disorder, and among the own diagnosis subgroups. However, contrary to our hypothesis, the number of SCID comorbid disorders was higher for respondents with an own diagnosis of bipolar disorder (1.4) compared to no diagnosis (0.3) (P=0.05).

Table 6.1 SCID diagnoses and own diagnoses, illness characteristics and comorbidity in 40 respondents with a SCID/DSM-IV diagnosis bipolar disorder

	SCID diagnosis				**Own diagnosis**				
	Bipolar I disorder (N=14)	**Bipolar II disorder (N=14)**	**Other bipolar disorder (N=12)**	**Significance**	**Bipolar disorder (N=5)**	**Depressive disorder (N=10)**	**Other diagnosis (N=18)**	**No diagnosis (N=7)**	**Significance**
SCID diagnosis									
- Bipolar I disorder (N=14)					4	2	7	1	NS
- Bipolar II disorder (N=14)	NA	NA	NA		1#	5	6	2	
- Other bipolar disorder (N=14)					0	3##	5##	4	
Own diagnosis									
- Bipolar disorder (N=5)	4	1#	0						
- Depressive disorder (N=10)	2	5	3##		NA	NA	NA	NA	
- Other diagnosis (N=18)	7	6	5##	NS					
- No diagnosis (N=7)	1	2	4						
Mean age (median)	46.1 (44.5)	41.3 (39.7)	44.2 (43.8)	NS	48.8 (48.5)	43.7 (44.1)	41.4 (41.6)	46.7 (42.4)	NS
Female %	64.3	50.0	75.0	NS	60.0	60.0	72.2	42.9	NS
Age first (hypo)manic episode (median) (N=34) a-e	33.0 (36.0) (N=14)	26.8 (22.0) (N=12) a	28.6 (28.0) (N=8) b	NS	35.4 (37) (N=5)	27.7 (22.0) (N=9) c	30.6 (33.0) (N=15) d	25.4 (21.0) (N=5) e	NS
Number of respondents (%) with									
- Symptoms prior to first episode (N=38) f-h	5/14 (35.7)	2/14 (14.3)	3/10 (30.0) f	NS	2/5 (40.0)	2/10 (20.0)	6/17 (35.3) g	0/6 (0.0) h	NS
- mean age (median)	16.8 (15.0)	14.0 (14.0)	21.7 (21.0)	NS	20 (20)	10.5 (10.5)	19.3 (16.5)	NA	NS
- Start with depressive episode (N=37) n-r	9/14 (64.3)	6/12 (50.0) i	3/12 (27.3) j	NS	2/5 (40)	4/9 (44.4) k	11/17 (64.7) l	1/6 (16.7) m	NS
- mean age (median)	20.7 (20.0)	28.7 (24.5)	25.3 (25)	NS	24 (24)	18.8 (18.5)	26.4 (25.0)	21.0 (21.0)	NS
Median number of mood episodes									
- Overall mood episodes (N=37) n-r	5 (N=13) n	>10 (N=14)	2 (N=10) o	NS	5 (N=5)	5 (N=9) p	5 (N=17) q	>10 (N=6) r	NS
- (Hypo)manic episodes (N=35) n-r	2 (N=13) n	>10 (N=14)	>10 (N=8) o	*P*=0.049 *	2 (N=5)	4 (N=8) p	2.5 (N=16) q	>10 (N=6) r	NS
- Depressive episodes (N=37) n-r	2 (N=13) n	3 (N=14)	1.5 (N=10) o	NS	3 (N=5)	2 (N=9) p	2 (N=17) q	9.5 (N=6) r	NS
Mean number of comorbid disorders (median)	0.9 (0.5)	0.9 (1.0)	0.4 (0.0)	NS	1.4 (1.0)	0.7 (0.5)	0.8 (0.0)	0.3 (0.0)	NS

* *SCID/DSM-IV diagnosis bipolar I disorder vs. SCID/DSM-IV diagnosis bipolar II disorder P=0.005*

\# *Respondent with bipolar II disorder and a manic episode induced by the use of antidepressant.*

\## *Respondent with hypomanic episode induced by the use of antidepressant.*

a *In two respondents age at the first hypomanic episode was unknown.*

b *Four respondents experienced (hypo)manic symptoms without meeting criteria for a (hypo)manic episode; therefore age at first (hypo)manic episode was not assessable.*
Two respondents (with cyclothymia) experienced (hypo)manic episodes "as long as they remembered"; age at first (hypo)manic episode was arbitrary set at 10 years.

c *One respondent experienced (hypo)manic symptoms without meeting criteria for a hypomanic episode; therefore age at first (hypo)manic episode was not assessable.*

d *In one respondent age at first hypomanic episode was unknown.*
Two respondents experienced (hypo)manic symptoms without meeting criteria for a (hypo)manic episode; therefore age at first (hypo)manic episode was not assessable.
One respondent (with cyclothymia) experienced (hypo)manic episodes "as long as he remembers"; age at first (hypo)manic episode was arbitrary set at 10 years.

e *In one respondent age at first hypomanic episode was unknown.*
One respondent experienced (hypo)manic symptoms without meeting the criteria for a (hypo)manic episode; therefore age at first (hypo)manic episode was not assessable.
One respondent (with cyclothymia) experienced (hypo)manic episodes "as long as he remembered"; age at first (hypo)manic episode was arbitrary set at 10 years.

f *Two respondents experienced (hypo)manic and depressive symptoms without meeting the criteria for a mood episode; therefore "symptoms prior to first episode" were not assessable.*

g *One respondent experienced (hypo)manic and depressive symptoms without meeting the criteria for a mood episode; therefore "symptoms prior to first episode" were not assessable.*

h *One respondent experienced (hypo)manic and depressive symptoms without meeting the criteria for a mood episode; therefore "symptoms prior to first episode" were not assessable.*

i *In two respondents age at first hypomania is unknown.*

j *In one respondent age at first hypomanic symptoms is unknown.*

k *In one respondent age at first hypomanic symptoms is unknown.*

l *In one respondent age at first hypomania is unknown.*

m *In one respondent age at first hypomania is unknown.*

n *In one respondent number of depressive and manic episodes was not assessed.*

o *In four respondents number of (hypo)manic episodes was not assessable because of experiencing (hypo)manic symptoms without meeting criteria for a (hypo)manic episode; in two of them number of depressive episodes was also not assessable because of not meeting the criteria for a depressive episode.*

p *In one respondent number of depressive and manic episodes was not assessed.*
One respondent experienced (hypo)manic symptoms without meeting criteria for a (hypo)manic episode; therefore number of (hypo)manic episodes was not assessable.

q *One respondent experienced (hypo)manic and depressive symptoms without meeting criteria for a mood episode or cyclothymia; therefore number of (hypo)manic and depressive episodes was not assessable.*
One respondent experienced (hypo)manic symptoms without meeting criteria for a (hypo)manic episode; therefore number of (hypo)manic episodes was not assessable.

r *One respondent experienced (hypo)manic and depressive symptoms without meeting criteria for a mood episode or cyclothymia; therefore number of (hypo)manic and depressive episodes was not assessable.*

NA *Not applicable*

NS *Not significant*

Consultation of health professionals (table 6.2)

The majority of the respondents (N=36, 90 %) had consulted their general practitioner for their problems at a mean age of 31.4 years (median 30 years). The most frequent reason to visit the general practitioner was depressive mood and anxiety (N=22, 61.1%). Of the respondents with a SCID diagnosis of bipolar II disorder or other bipolar disorder, 69.9% consulted the general practitioner with depressive mood and anxiety compared to 46.2% of the respondents with a SCID diagnosis bipolar I disorder (NS). The reasons why respondents (N=4) did not seek contact with their general practitioner were: "These periods [with (hypo)manic episodes] are pleasant, productive and part of my personality" (N=3) while one respondent came straight into contact with a psychiatrist because of a psychosis post partum. Respondents who thought they had no diagnosis had sought significantly less help from their general practitioner than the other own diagnosis groups (P=0.033).

Twenty-five respondents (62.5%) had consulted a mental health care professional at a mean age of 31.4 years (median 33 years). The most frequent reason to go to a mental health care professional was depressive mood and anxiety (N=14, 56%). Twenty-two (84.6%)of respondents with bipolar II disorder or other bipolar disorder consulted a mental health care professional with depressive mood and anxiety compared to 25% of the respondents with a SCID diagnosis bipolar I disorder (NS, P=0.06). The reasons why respondents did not consult mental health care (N=15) were: treatment by the general practitioner (N=7); no trust in mental health care (N=4); "These periods [with (hypo)manic episodes] are pleasant, productive and part of my personality" (N=3); or "It was not necessary" (N=1). There were indications that a less severe diagnosis was associated with less seeking for mental health care. Both the subgroup of other SCID diagnoses and of no own diagnosis sought less help than the other subgroups of SCID diagnoses (P=0.024) and own diagnoses (P=0.044), respectively.

In total eight respondents had needed hospitalization or day treatment, for the first time at a mean age of 36.1 years (median 38.5 years). Significantly more of these respondents had a SCID diagnoses bipolar I disorder (P=0.003).

Treatment history (table 6.2)

Fourteen (35%) respondents never used medication for their mood problems. Medication was ever used by 12 of the 14 respondents with SCID bipolar I disorder (85.7%) and by 6 of 14 (42.9%) with bipolar II disorder. Of the own diagnoses subgroups all respondents with own diagnosis bipolar disorder had used medication, compared to only 2 of 7 (28.6%) with no diagnosis .The differences between the various subgroups were not significant.

With regard to individual medications, only five respondents had used a mood stabilizer, who were all the respondents with an own diagnosis of bipolar

disorder (*P*=0.000 compared to the other subgroups of own diagnosis). Seven (17.5%) respondents had used an antipsychotic. All of them had a SCID diagnosis bipolar I disorder, which corresponds to 50% of this subgroup and is significantly more than the other SCID diagnosis subgroups (*P*=0.000). The use of an antipsychotic was also significantly higher (N=3, 60%) in the subgroup with an own diagnosis of bipolar disorder compared to the other subgroups of own diagnoses (*P*=0.021). Antidepressants and sedative medication (anxiolytics or hypnotics) had been used by 16 (40%) and 19 (47.5%) respondents, respectively. There were no significant differences in the use of antidepressants or sedatives between the various subgroups.

More than half of the respondents (N=21, 52.5%) reported having received psychological treatment. Only the subgroup of SCID bipolar I disorder was significantly associated with more psychological treatment (*P*=0.045). All respondents with an own diagnosis of bipolar disorder had received psychological treatment; four reported frequent visits at a psychiatrist, one reported frequent visits at a psychologist and when necessary consultation of a psychiatrist, three had received psychoeducation and one had received creative therapy.

Costs (table 6.3)

As shown in table 6.3, the direct medical costs generated by respondents with SCID diagnosis bipolar I disorder (€1539) were significantly higher than those generated by respondents with bipolar II disorder (€423; *P*=0.004) and other bipolar disorder (€721; *P*=0.038; overall *P*=0.012). Overall the differences in direct medical costs between the subgroups of own diagnosis were not significant (*P*= 0.06). Respondents with an own diagnosis of bipolar disorder generated non-significantly higher direct costs (€1983) than the other subgroups of own diagnosis. Interestingly, also the respondents with no diagnosis generated high direct costs (€1048). The majority of the 40 respondents (N=30, 75%) had a paying job. The only subgroup with significantly fewer paying jobs were the respondents with an own diagnosis of bipolar disorder (N=1, 20%; *P*=0.021). The differences in mean indirect costs and total costs between the subgroups of SCID diagnoses or own diagnoses were not significant, although the indirect costs generated by the respondents with no diagnosis were high (€6146).

Table 6.2 Consultation of health professionals and treatment history in 40 respondents with SCID/DSM-IV diagnosis bipolar disorder categorized by subtype of SCID diagnosis and own diagnosis

	SCID diagnosis				**Own diagnosis**				
	Bipolar I disorder (N=14)	**Bipolar II disorder (N=14)**	**Other bipolar disorder (N=12)**	**Significance**	**Bipolar disorder (N=5)**	**Depressive disorder (N=10)**	**Other diagnosis (N=18)**	**No diagnosis (N=7)**	**Significance**
Number of respondents (%) who consulted									
- General practitioner	13 (92.9)	13 (92.9)	10 (83.3)	NS	5 (100)	10 (100)	17 (94.4)	4 (57.1)	*P*=0.033
- mean age (median)	30.3 (29)	30.8 (30)	33.4 (34.5)	NS	30.8 (29)	28.9 (29.5)	31.7 (29)	37 (35)	NS
- Mental health care	12 (85.7)	9 (64.3)	4 (33.3)	*P*=0.024	5 (100)	8 (80)	10 (55.6)	2 (28.6)	*P*=0.044
- mean age (median)	33.1 (35.5)	28.3 (30)	33.5(39)	NS	34 (36)	30.5 (31.5)	29.1 (28)	40.5 (40.5)	NS
Number of respondents (%) with hospitalization or day treatment	7 (50)	1 (7.1)	0	*P*=0.003	3 (60)	1 (10)	4 (22.2)	0	NS
- mean age (median)	37 (40)	30 (30)	NA	NS	39.7 (40)	50 (50)	30 (29.5)	NA	NS
Number of respondents (%) who used									
- Ever medication	12 (85.7)	6 (42.9)	8 (66.7)	NS	5 (100)	7 (70)	12 (66.7)	2 (28.6)	NS
- Mood stabilizer	4 (28.6)	1 (7.1)	0	NS	5 (100)	0	0	0	*P*=0.000
- Antipsychotic	7 (50)	0	0	*P*=0.000	3 (60)	0	4 (22.2)	0	*P*=0.021
- Antidepressant	7 (50)	5 (37.5)	4 (33.3)	NS	3 (60)	5 (50)	7 (38.9)	1 (14.3)	NS
- Sedative	10 (71.4)	4 (28.6)	5 (41.7)	NS	5 (100)	5 (50)	7 (38.9)	2 (28.6)	NS
Number of respondents (%) who received									
- Psychological treatment	11 (78.6)	6 (42.9)	4 (33.3)	*P*=0.045	5 (100)	5 (50)	9 (50)	2 (28.6)	NS

NA *Not applicable*
NS *Not significant*

Table 6.3 Mean direct costs and indirect costs in 40 respondents with a SCID/DSM-IV diagnosis bipolar disorder categorized by subtype of SCID diagnosis and own diagnosis

	SCID diagnosis				**Own diagnosis**				
	Bipolar I disorder (N=14)	**Bipolar II disorder (N=14)**	**Other bipolar disorder (N=12)**	**Significance**	**Bipolar disorder (N=5)**	**Depressive disorder (N=10)**	**Other diagnosis (N=18)**	**No diagnosis (N=7)**	**Significance**
Number of respondents (%) with paying work	8 (57.1)	12 (85.7)	10 (83.3)	NS	1 (20)	8 (80)	16 (88.9)	5 (71.4)	*P*=0.021
Mean costs per year (Euro)									
- Direct (N=40)	1539	423	721	*P*=0.012 **	1983	475	785	1048	NS
- Indirect (N=30) *	2852 (N=8)	3747 (N=12)	3706 (N=10)	NS	0 (N=1)	1593 (N=8)	3835 (N=16)	6146 (N=5)	NS
- Total	3169	3635	3809	NS	1983	1749	4194	5438	NS

* *Only calculated for respondents with paying job.*

** *SCID/DSM-IV diagnosis bipolar I disorder vs. SCID/DSM-IV diagnosis bipolar II disorder P=0.004*
SCID/DSM-IV diagnosis bipolar I disorder vs. SCID/DSM-IV diagnosis other bipolar disorder P=0.038

NS *Not significant*

Discussion

In this group of 40 respondents with a lifetime SCID/DSM-IV diagnosis of bipolar disorder, only 5 (12.5%) had been recognized as such by mental health care professionals and did agree with their diagnosis. Only these 5 respondents used a mood stabilizer (lithium or an anticonvulsant) and received psychological treatment. All other 35 respondents (87.5%) were not aware of having a bipolar disorder. Ten (25%) respondents thought they had a depressive disorder, 18 (45%) another disorder and 7 (17.5%) were convinced that they had no disorder at all. Similar data of low recognition and misdiagnosis were found in a study among the 600 members of the US National Depressive and Manic-Depressive Association with a bipolar disorder (Hirschfeld et al., 2003*b*). Almost 70% of the members reported having been misdiagnosed and having received a mean of 3.5 other diagnoses. The most common incorrect diagnosis was unipolar depression (60%), other frequently reported misdiagnoses were anxiety disorder (26%), schizophrenia (18%), borderline or antisocial personality disorder (17%), alcohol or substance abuse (14%) and schizoaffective disorder (11%).

The majority of our bipolar respondents had sought help from their general practitioner (N=36, 90%) and from a mental health care professional (N=25, 69.4%). Nevertheless, only 5 of them had received the correct diagnosis. The low recognition of bipolar disorder among the respondents who had sought help from their general practitioner (5/36, 13.6%) or from mental health care (5/25, 20%) is comparable with previous findings in clinical samples although these samples included patients presenting with depression (Manning et al., 1997; Hantouche et al., 1998; Ghaemi et al., 1999; Ghaemi et al., 2000; Hirschfeld et al., 2005; Manterre et al., 2004)).

The present study on the rate of recognition and treatment of bipolar disorder has several strengths. First, it was performed in a sample recruited from the general population rather than in a clinical sample like the previous studies in general practice and mental health care settings. This gave us the unique opportunity to identify people with bipolar disorder who were given another diagnosis or who had never sought help and/or thought they had no disorder at all. The sample is not biased by the filters of the Goldberg-Huxley model. The only selection bias applicable was refusal to participate in the original NEMESIS study and the reappraisal study. The participants of NEMESIS reflect the Dutch population accurately (Bijl et al., 1998*a*). The participants of the subsequent reappraisal study were significantly older, higher educated and more employed than the non-participants (Regeer et al., 2004). However, we assume that our sample is still representative for the whole NEMESIS population. The most common reason in NEMESIS for drop-out was failure to locate the respondent, while psychopathology had only moderate effects on attrition and morbidity/mortality but not to refusal (de Graaf et al., 2000). Second, in the present study respondents were interviewed by clinicians

with a semi-structured interview (SCID) and questioned in detail about help-seeking patterns, recognition and received treatments. This is in contrast to previous studies in the general population that were performed by trained lay interviewers with a fully structured interview (CIDI) or a screening instrument (MDQ) and that only globally asked about diagnostics and treatment. Third, respondents were asked about their subjective opinion of their diagnosis.

Our data support the hypothesis that self-recognition is probably the most important factor for treatment seeking and receiving adequate treatment. Only the five (12.5%) respondents who had been recognized with bipolar disorder by a mental health care professional and did agree with this diagnosis used a mood stabilizer (lithium or an anticonvulsant). The respondents who thought they had no diagnosis sought significantly less help from their general practitioner and from mental health care than the other subgroups of own diagnosis. Subgroups of SCID diagnosis bipolar disorder were not associated with consulting the general practitioner. However the subgroup SCID diagnosis other bipolar disorder sought less help from mental health care than the other subgroups of SCID diagnosis

In contrast to our a priori hypothesis self-recognition was not significantly associated with any subtype of bipolar disorder. Although four of the five respondents with a recognized bipolar disorder had a SCID diagnosis bipolar I disorder, the other 10 respondents with a SCID diagnosis bipolar I disorder did not report a diagnosis of bipolar disorder. However, only one respondent with SCID diagnosis bipolar I disorder believed that he suffered from no disorder at all.

The most common reasons to consult a mental health care professional were anxiety and depression problems, especially for the respondents with a SCID diagnosis bipolar II disorder or bipolar disorder NOS. This is in line with the findings in a clinical sample of 203 outpatients who presented with a major depression in a private psychiatric clinic (Benazzi, 1997). In that study, a substantial number of the depressed patients were diagnosed with bipolar disorder (45% had bipolar II disorder and 4% bipolar I disorder). In addition, more than half (60%) of the members of the US National Depressive and Manic-Depressive Association with bipolar disorder sought treatment because of depression (Hirschfeld & Vornik, 2004). Apparently hypomanic symptoms did not trigger treatment seeking behaviour because people do not recognize hypomanic episodes as dysfunctional; they experience hypomanic symptoms as pleasant and productive or as a normal feature of their personality.

The total number of mood episodes, number of depressive episodes and (hypo)manic episodes between the respondents with a recognized bipolar disorder and the other own diagnosis groups was not significantly higher indicating that this did not influence recognition. The median number of (hypo)manic episodes experienced by respondents with a SCID diagnosis bipolar I disorder was significant less than in

the other subgroups of SCID diagnosis. However, counting the number of episodes in the subgroup other bipolar disorder was inconsistent; the number of (hypo)manic and depressive episodes in respondents with cyclothymia were counted although these do not meet the DSM-IV criteria for an episode, in case of brief hypomania or periods with manic symptoms without meeting the criteria for an episode the number of episodes were not counted.

Our data did not support the hypothesis that the presence of comorbid psychiatric disorders hampers recognition of bipolar disorder. On the contrary, the number of SCID comorbid disorder tended to be higher for respondents with own diagnosis bipolar disorder compared to no diagnosis. Suffering from more than one disorder probably increases the agony and as a consequence also help-seeking behaviour. A retrospective study comparing treatment patterns and costs for patients with recognized and unrecognized bipolar disorder, based on managed care claims, also found significantly higher rates of comorbidity among recognized bipolar patients (Birnbaum et al., 2003).

The finding that significantly less respondents with a recognized bipolar disorder had a paying job indicates that in these respondents the disorder interferes with daily functioning and performing a job. In a recent cross-national analysis among 968 members of an advocacy organization for bipolar disorder in eight European countries, comparable low employment levels varying from 27.1% to 56.4 % were found (Morselli et al., 2004). In line with our expectation, indirect costs were non-significantly higher in respondents with an unrecognized bipolar disorder. This can be partly explained by the fact that indirect cost are based on respondents with a paying job and only one respondent with a recognized bipolar disorder had a paying job. Indirect costs generated by respondents who suffered from no disorder were also high (€6146). It is therefore clear that also these respondents, despite that they sought significantly less help, suffer from serious mental problems that lead to impairment.

There were no significant differences in indirect cost between the subtypes of SCID diagnoses indicating that the most severe type of bipolar disorder, bipolar I disorder, did not lead to more reduced efficiency and more days of absence than the less severe subtypes. However, this can also partly be explained by the fact that the indirect cost were based on respondents with a paying job and only 57.1% of the respondents with a SCID diagnosis bipolar I disorder had a paying job.

Significant more respondents with bipolar I disorder consulted a mental health care professional, used antipsychotics, received psychological treatment, day treatment or were hospitalized, resulting in a significant higher amount of direct medical costs than in the other subtypes of SCID diagnosis. Respondents with a recognized bipolar disorder generated non-significantly higher direct medical cost than respondents with unrecognized bipolar disorder.

Limitations

Our study has several limitations. First, a small number of respondents participated in the study, which is inevitable when respondents are recruited from the general population and the prevalence of a disease is low. Due to the small numbers the current paper is mainly descriptive. However, the present results may give directions for future research on factors related to recognition and receiving adequate treatment. Second, the data were based on retrospective recall of lifetime diagnosis of bipolar disorder. Probably relatively severe symptoms and episodes that lead to impairment and treatment seeking will be remembered. Related to this recall bias is the fact that no significant others were interviewed and diagnoses of bipolar disorder was only based on self-report of episodes. Therefore, underdiagnosis of hypomania probably has occurred. Finally, data on received former diagnosis and treatment were based on report of the respondents and not verified at their health care professionals. Possibly some of the respondents have received the diagnosis of bipolar disorder but have forgotten it or have denied the diagnosis. Therefore the actual percentage of underrecognition by general practitioners and mental health care professionals may be lower than found in this study. Nevertheless we assume that the rates of underdiagnosis we found based on self-report are representative of the diagnostic process in everyday practice. This assumption is based on the similar rates found in studies in general practice and mental health care settings (Manning et al., 1997; Hantouche et al., 1998; Ghaemi et al., 1999; Ghaemi et al., 2000; Hirschfeld et al., 2005; Manterre et al., 2004)).

Clinical implications

In contrast to our a priori hypotheses, comorbidity and severity of bipolar disorder, expressed by type of bipolar disorder and number of episodes did not impair its recognition. Self-recognition appears to be the most important factor in treatment seeking and receiving adequate treatment. This stresses the importance of paying attention to awareness and acceptance when the diagnosis of bipolar disorder is made. Studies have shown positive effects of psychoeducation and psychological treatment (i.e. cognitive behavioural therapy, interpersonal social rhythm therapy and family-focused therapy) on acceptance of the diagnosis and compliance (Perry et al., 1999; Colom et al., 2003; Lam et al., 2003; Miklowitz et al., 2003; Frank et al., 2005; Miklowitz, 2006). In addition, retrospective and prospective mood charting could be helpful in improving insight in the illness and adherence to therapy (Baldassano, 2005).

In our study about half of the respondents reported that their illness had started with a depressive episode or with depressive symptoms, and most respondents had sought treatment for depressive mood and anxiety. Probably because overactivity, euphoria or irritability were not thought of as pathological symptoms and were often experienced as ego-syntonic, most respondents did not consult a mental health

care professional for these symptoms. Therefore, general practitioners and mental health care professionals should always consider bipolar spectrum disorder and ask about a history of (hypo)mania in patients presenting with depression or anxiety. Indicators of bipolarity in patients presenting with depression are early age of onset (< age 25), atypical depressive features, brief major depressive disorder (on average < 3 months), rapid on/off pattern, seasonality, more than three major depressive episodes, psychotic symptoms, postpartum depression, wearing off of antidepressant efficacy, lack of response to three or more antidepressant treatment trials, hyperthymic personality at baseline and family history of bipolar disorder (Ghaemi et al., 2002; Berk & Dodd et al., 2005, Kaye, 2005; Suppes et al., 2005; Perlis et al., 2006).

In conclusion, this study showed that most people seek treatment for depressive symptoms and that self-recognition of bipolar disorder is an important factor for receiving adequate treatment. Therefore, clinicians should explore possible former (hypo)manic episodes in patients presenting with a depression and once a diagnosis of bipolar disorder is made special attention should be paid to awareness and acceptance of the diagnosis.

References

Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L. Antidepressant-induced Mania and Cycle Acceleration: A Controversy Revisited. Am J Psychiatry 1995;152:1130-1138.

Baldassano CF. Assessment tools for screening and monitoring bipolar disorder. Bipolar Disord 2005;7(Suppl. 1):8-15.

Benazzi F. Prevalence of bipolar II disorder in outpatient depression: a 203-case study in private practice. J Affect Disord 1997;43:163-166.

Berk M, Dodd S. Bipolar II disorder: a review. Bipolar Disord 2005;7:11-21.

Birnbaum HG, Shi L, Dial E, Oster EF, Greenberg PE, Mallett DA. Economic Consequences of Not Recognizing Bipolar Disorder Patients: A Cross-Sectional Descriptive Analysis. J Clin Psychiatry 2003;64:1201-1209.

Bijl RV, Zessen G van, Ravelli A, de Rijk C, Langendoen Y.. The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. Soc Psychiatry Psychiatr Epidemiol 1998*a*;33:581-586.

Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 1998*b*;33:587-595.

Calabrese JR, Hirschfeld RM, Reed M, Davies MA, Frye MA, Keck PE, Lewis L, McElroy SL, McNulty JP, Wagner KD. Impact of Bipolar Disorder on a U.S. community sample. J Clin Psychiatry 2003;64:425-432.

Colom F, Vieta E, Martinez-Aran A, Reinares M, Goikolea JM, Benabarre A, Torrent C, Comes M, Corbella B, Parramon G, Corominas J. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Arch Gen Psychiatry 2003;60:402-407.

Das AK, Olfson M, Gameroff MJ, Pilowsky DJ, Blanco C, Feder A, Gross R, Neria Y, Lantigua R, Shea S, Weissman MM. Screening for bipolar disorder in a primary care practice. JAMA 2005;293:956-963.

Dunner DL. Clinical consequences of under-recognized bipolar spectrum disorder. Bipolar Disord 2003;5:456-463.

Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagiolini AM, Grochocinski V, Houck P, Scott J, Thompsom W, Monk T. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Arch Gen Psychiatry 2005;62:996-1004.

Ghaemi SN, Sachs GS, Chiou AM, Pandurangi AK, Goodwin F. Is bipolar disorder still underdiagnosed? are antidepressants overutilized? J Affect Disord 1999;52:135-144.

Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing Bipolar Disorder and the effects of Antidepressants: A Naturalistic Study. J Clin Psychiatry 2000;61:804-808.

Ghaemi SN, Lenox MS, Baldessarini RJ. Effectiveness and safety of long-term antidepressant treatment in bipolar disorder. J Clin Psychiatry 2001;62:565-569.

Ghaemi SN, Ko JY, Goodwin FK. " Cade's Disease" and Beyond: Misdiagnosis, Antidepressant Use, and a Proposed Definition for Bipolar Spectrum Disorder. W Can J Psychiatry 2002;47:125-134.

Goldberg D, Huxley P. Mental illness in the community. The pathway to psychiatric care. Tavistock Publications, London and New York, 1980.

Goldberg D, Huxley P. Common mental disorders. Tavistock/Routledge, London, 1992.

Goodwin FK, Jamison KR, Manic-depressive illness. Bipolar Disorder and Recurrent Depression, second edition, Oxford University Press, New York 2007.

Graaf R de, Bijl RV, Smit F, Ravelli A, Vollebergh WAM. Psychiatric and Sociodemographic Predictors of Attrition in a Longitudinal Study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Am J Epidemiol 2000;152:1039-1047.

Hakkaart- van Roijen L. Manual Trimbos/iMTA questionnaire for costs associated with psychiatric illness (in Dutch). Institute for Medical Technology Assessment, Rotterdam, 2002.

Hakkaart-van Roijen L. Hoeijenbos MB, Regeer EJ, ten Have M, Nolen WA, Veraart CPWM, Rutten FFH. The societal cost and quality of life of patients suffering from bipolar disorder in the Netherlands. Acta Psychiatr Scand 2004;110:383-392.

Hantouche EG, Akiskal HS, Lancrenon S, Allilaire JF, Sechter D, Azorin JM, Bourgeois M, Fraud JP, Chatenet-Duchene L. Systematic clinical methodology for validating bipolar-II disorder: data in mid-stream from a French national multi-site study (EPIDEP). J Affect Disord 1998;50:163-173.

Have M ten, Vollebergh W, Bijl R, Nolen WA. Bipolar disorder in the general population. Prevalence, consequences and care utilisation: results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). J Affect Disord 2002;68:203-213.

Hirschfeld RMA. Bipolar Spectrum: Improving Its Recognition and Diagnosis. J Clin Psychiatry 2001;62(Suppl. 14):5-9.

Hirschfeld RM, Calabrese JR, Weissman MM Reed M, Davies MA, Frye MA, Keck PE, Lewis L, McElroy SL, McNulty JP, Wagner KD. Screening for Bipolar Disorder in the Community. J Clin Psychiatry 2003*a*;64:53-59.

Hirschfeld RM, Lewis LL, Vornik LA. Perceptions of Bipolar Disorder: How Far Have we Really Come? Results of the National Depressive and Manic-Depressive Association 2000 Survey of Individuals with Bipolar Disorder. J Clin Psychiatry 2003*b*;64:161-174.

Hirschfeld RM, Holzer C, Calabrese JR, Weissman M, Reed M, Davies M, Frye MA, Keck P, McElroy S, Lewis L, Tierce J, Wagner KD, Hazard E. Validity of the Mood Disorder Questionnaire: A General Population Study. Am J Psychiatry 2003*c*;160:178-180.

Hirschfeld RM, Vornik LA. Recognition and diagnosis of bipolar disorder. J Clin Psychiatry. 2004;65(Suppl. 15):5-9.

Hirschfeld RM, Cass AR, Holt DCL, Carlson CA. Screening for Bipolar disorder in patients treated for depression in a family medicine clinic. J Am Board Fam Pract 2005;18:233-239.

Kaye NS. Is your depressed patient bipolar? J Am Board Fam Pract 2005;18:271-81.

Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med 1997;27:1079-1089

Lam DH, Watkins ER, Hayward P, Bright J, Wright K, Kerr N, Parr-Davis G, Sham P. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. Arch Gen Psychiatry 2003;60:145-152.

Mantere O, Suominen K, Leppämäki S, Valtonen S, Arvilommi P, Isometsä E. The clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS), Bipolar Disord 2004;6:395-405.

Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RMA. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. J Affect Disord 1994;31:281-294.

Manning JS, Haykal RF, Connor PD, Akiskal HS. On the nature of depressive and anxious states in a family practice setting: the high prevalence of bipolar II and related disorders in a cohort followed longitudinally. Compr Psychiatry 1997;38:102-108.

Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry 2003;60:904-912.

Miklowitz DJ. A review of Evidence-Based Psychosocial Interventions for Bipolar Disorder. J Clin Psychiatry 2006;67(Suppl. 11):28-33.

Miller CJ, Klugman J, Berv DA, Rosenquist KJ, Ghaemi SN. Sensitivity and specificity of the Mood Disorder Questionnaire for detecting bipolar disorder. J Affect Disord 2004;8:167-171.

Morselli PL, Elgie R. GAMIAN-Europe/BEAM survey I: global analysis of a patient questionnaire circulated to 3450 members of 12 European advocacy groups operating in the field of mood disorders. Bipolar Disord 2003;5:265-278.

Morselli PL, Elgie R, Cesana BM. GAMIAN-Europe/BEAM survey II: cross-national analysis of unemployment, family history, treatment satisfaction and impact of the bipolar disorder on life style. Bipolar Disord 2004;6:487-497.

Perlis RH, Brown E, Baker RW, Nierenberg AA. Clinical Features of Bipolar Depression Versus Major Depressive Disorder in Large Multicenter Trials. Am J Psychiatry 2006;163:225-231.

Perry A, Tarrier N, Morris R, McCarthy E, Limb K. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. BMJ 1999;318:149-153.

Regeer EJ, ten Have M, Rosso ML, Hakkaart-van Roijen L, Vollebergh W, Nolen WA. Prevalence of bipolar disorder in the general population: A reappraisal study of the Netherlands Mental Health and Incidence Study; Acta Psychiatr Scand 2004;110:374-382.

Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK. The de facto US mental and addictive disorders service system. Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry 1993;50:85-94.

Sachs GS, Koslow CL, Ghaemi SN. The treatment of bipolar depression. Bipolar Disord 2000;2:256-260.

Schaffer A, Cairney J, Cheung AH, Veldhuizen S, Levitt AJ. Use of Treatment Services and Pharmacotherapy for Bipolar Disorder in a general Population-Based Mental health Survey. J Clin Psychiatry 2006;67:386-393.

Spitzer LR, Williams JBW, Gibbon M, First MB. The Structured Clinical Interview for DSM-II-R (SCID) I: History, Rationale, and Description. Arch Gen Psychiatry 1992;49:624-629.

Suppes T, Leverich GS, Keck PE, Nolen WA, Denicoff KD, Altshuler LL, McElroy, Rush JA, Kupka R, Frye MA, Bickel M, Post RM. The Stanley Foundation Bipolar Treatment Outcome Network II. Demographics and illness characteristics of the first 261 patients. J Affect Disord 2001;67:45-59.

Suppes T, Kelly DI, Perla JM, Challenges in the Management of Bipolar Depression. J Clin Psychiatry 2005;66(Suppl. 5):11-16.

Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-Month Use of Mental Health Services in the United States. Arch Gen Psychiatry 2005;62:629-640.

Weber Rouget B, Gervasoni N, Dubuis V, Gex-Fabry M, Bondolfi G, Aubry JM. Screening for bipolar disorder using in a French version of the Mood Disorder Questionnaire (MDQ). J Affect Disord 2005;88:103-108.

Wittchen HU. Continued Needs for Epidemiological Studies of Mental Disorders in the Community. Psychother and Psychosom 2004;73:197-206.

Appendix A:

Questionnaire on diagnosis, recognition and treatment history

In respondents identified with bipolar disorder or major depressive disorder:

- When did they have their first psychological complaints/problems, and what were those problems?
- Do they recognize themselves that they have or have had psychological problems?
  - If they do not recognize it themselves: what are their explanations for their problems/symptoms?
- When did they for the first time consult a (mental) health professional for their psychological problems
  - If they did not consult a (mental) health professional: why not?

In respondents identified with bipolar disorder based on the SCID:

- Do they recognize themselves that they have or have had depressive episodes and (hypo)manic episodes, respectively?
  - If they do not recognize it themselves: what are their explanations for their problems/symptoms?
- When did they have their first depressive episode?
  - When did they for the first time consult a (mental) health professional for this (or later) episode; and which diagnosis was made; if not: why not?
- When did they have their first (hypo)manic episode?
  - When did they for the first time consult a (mental) health professional for this (or later) episode; and which diagnosis was made; if not: why not?
- When (at what age) was the diagnosis of BPD made for the first time?

- Did they ever receive treatment? If yes: when (at what age) for the first time
  - Psycho-education
  - Psychotherapy
  - Medication: (separately for mood stabilizers, antipsychotics, antidepressants, anti-anxiety drugs (benzodiazepines), hypnotics)
  - Other treatments

CHAPTER 7

General discussion

Manic-depressive insanity comprehends, on the one hand, the entire domains of so-called periodic and circular insanity, and, on the other, simple mania usually distinguished from the above. Over the course of years I have become more and more convinced that all the pictures mentioned are merely forms of one single disease process. (…) It is, as far as I can see, quite impossible to find boundaries between the single disease pictures that have so far been kept apart. From "simple" mania, the numerous cases with 2, 3, 4 attacks in a lifetime lead quite gradually over to periodic forms, and from these we reach circular insanity, through those cases in which a more and more marked initial or terminal stage of depression gradually complicates the pure picture of mania, or in which the long series of maniacal attacks is unexpectedly interrupted by a state of depression.

(Translated from: *Psychiatrie. Ein Lehrbuch Für Studirende und Aerzte* by Kraepelin, 1899 p359-360)

In 1899 in the sixth edition of his textbook, Emil Kraepelin introduced the term manic-depressive insanity (*das manisch-depressive Irresein*). Within this term he included almost all forms of affective disorders: a common form with recurrent, severe, classic depressive episodes and a less common form alternating between mania and depressions, sometimes with mixed, agitated-dysphoric states. Nearly two-thirds of his sample of over 400 cases involved recurrent depression and one-third involved a bipolar course. In Kraepelin's concept, mood disorders had a common root with gradual transitions between individual forms without sharp boundaries (Kraepelin, 1921).

Recapitulation of research questions

The main aims of this thesis were to study the expressions of bipolar mood disorders, its consequences, the diagnostic process, and recognition and treatment rates in a sample of respondents recruited from the general population.

More specifically, the main questions of this thesis were the following:

1. What is the prevalence of bipolar spectrum disorder among respondents in the general population with a diagnosis of bipolar disorder based on a fully structured interview (CIDI) when re-interviewed with a semi-structured interview (SCID) administered by clinicians? Which factors can explain the discrepancies between diagnoses based on the CIDI and the SCID? Is a possible overdiagnosis of bipolar disorder explained by the presence of a cluster B personality disorder? (chapter 2)

2. What are the disorder-related societal costs and quality of life in respondents with a bipolar spectrum disorder in the general population? (chapter 3)
3. Is there a relationship between the subthreshold and clinical expression of mood disorders over time (chapter 4)
4. Do manic and depressive dimensions independently contribute to the use of mental health services? What is the degree of comorbidity between manic and depressive dimensions in respondents with and without mental health service use? (chapter 5)
5. What is the degree of recognition and treatment among respondents with a bipolar spectrum disorder in the general population, and what are determinants for underdiagnosis and undertreatment? (chapter 6)

Comparison of CIDI and SCID diagnoses

In NEMESIS, 158 (2.4%) respondents were identified with a CIDI/ DSM-III-R lifetime diagnosis of bipolar disorder at any of the three assessment points, 115 of them had participated in all three interviews, and 105 of them had indicated that they could be contacted in case of follow-up studies. Ultimately, 74 (70.5%) of these 105 respondents participated in our reappraisal study, i.e., 46.8% of the total sample with a bipolar disorder. In order to keep the interviewers blind for the original CIDI/DSM-III-R diagnosis, a second group of 57 respondents with a lifetime diagnosis of major depressive disorder was selected. These 57 were randomly selected out of all respondents with major depressive disorder (N=1403) of whom 1002 had participated in all three interviews, and 894 had agreed to participate in case of a follow-up study. Finally, 40 (70%) respondents participated in the reappraisal study. All these 114 respondents were re-interviewed by clinicians with the SCID.

The SCID distinguishes several DSM-IV subtypes of bipolar disorder: bipolar I disorder, bipolar II disorder, bipolar disorder NOS and cyclothymia. In addition a separate DSM-IV category 'mood disorder induced by substance use, specified with depressive, manic or mixed characteristics' is distinguished. Hereafter all these different disorders will be named "bipolar spectrum disorder".

Thirty (40.5%) of all 74 respondents with a CIDI/DSM-III-R bipolar disorder met the criteria for a SCID/DSM-IV bipolar spectrum disorder (see chapter 2, table 2.1). Of the 49 respondents with a CIDI/DSM-III-R bipolar I disorder, 19 (38.8%) were diagnosed with a DSM-IV bipolar spectrum disorder by the SCID, including 11 (22.4%) with a DSM-IV bipolar I disorder. Of the 25 respondents with a CIDI/DSM-III-R bipolar disorder NOS, 11 (44%) had a SCID/DSM-IV diagnosis of bipolar spectrum disorder . The majority (70.5%) of the 44 respondents who were not diagnosed by the SCID with a DSM-IV

bipolar spectrum disorder met the criteria for a lifetime depressive disorder.

Eight of the 40 respondents with a CIDI/DSM-III-R diagnosis of major depressive disorder (20%) fulfilled the criteria for a SCID/DSM-IV bipolar spectrum disorder as well as two other respondents (5%) who had developed their first hypomanic episode in the two years between the last CIDI interview of the NEMESIS and the SCID interview (see chapter 2, table 2.2). These two respondents were not included in the estimation of the prevalence based on the SCID diagnoses.

In total, 40 respondents met the criteria for a DSM-IV/SCID diagnosis of bipolar spectrum disorder: 14 respondents with bipolar I disorder, 14 with bipolar II disorder (including one who developed a manic episode during the use of an antidepressant), 7 with bipolar disorder NOS, 3 with cyclothymia and 2 with bipolar disorder substance (antidepressant) induced (hereafter the latter three groups are referred to as "other bipolar disorder").

Prevalence of bipolar spectrum disorder

Based on the percentages of SCID/DSM-IV bipolar spectrum disorder among respondents with a CIDI/DSM-III-R bipolar disorder (1.0%; 95% CI: 0.7-1.3) or major depressive disorder (4.2%; 95% CI: 1.6-6.9), we calculated a lifetime prevalence of DSM-IV bipolar spectrum disorder of 5.2% (95% CI: 2.2-8.1), including 2% (95% CI: 0.1-4.1) for bipolar I disorder (see chapter 2, table 2.3). The small number of respondents, especially the number of respondents with a CIDI diagnosis of major depressive disorder, led to relatively large 95% CI of the estimated prevalence of SCID bipolar spectrum disorder in this group.

This high prevalence is in line with other recent studies in which percentages for lifetime bipolar spectrum disorder varied between 4.4% and 11%, depending on the criteria used (see chapter 1, table 1.4) (Szadoczky et al., 1998; Angst et al., 2003*a*; Judd & Akiskal 2003; Moreno & Andrade, 2005; Faravelli et al., 2006; Merikangas et al., 2007).

Discrepancies between mood diagnoses based on the CIDI and the SCID

Our reappraisal study (chapter 2) showed that compared to clinical diagnoses made with the SCID, the CIDI may represent both false positive and false negative results. Less than half (40.5%) of the respondents with a CIDI/DSM-III-R diagnosis of bipolar disorder fulfilled the criteria for a SCID/DSM-IV diagnosis of bipolar spectrum disorder. Rather,

unexpectedly 20% of the respondents in our reappraisal sample with a CIDI/DSM-III-R diagnosis major depressive disorder were diagnosed by the SCID with a DSM-IV bipolar spectrum disorder.

We found no clear explanation for the discrepancy between the CIDI/DSM-III-R and SCID/DSM-IV diagnoses (see chapter 2, table 2.4). The differences in the minimal duration of the (hypo)manic episode asked for in the CIDI (2 days) versus the SCID (4 days) did not explain the over diagnosis of bipolar disorder by the CIDI. Based on CIDI interviews, 80% of the respondents with a CIDI/DSM-III-R and SCID/DSM-IV diagnosis of bipolar spectrum disorder indicated that their longest (hypo)manic episode had lasted 4 days or more. Over eighty-five percent (86.4%) of the respondents with a CIDI/DSM-III-R diagnosis of bipolar disorder but no SCID/DSM-IV diagnosis of bipolar spectrum disorder reported a (hypo)manic episode of 4 days or more.

We also found no indications that the more severe cases of bipolar disorder were diagnosed both by the CIDI and the SCID. Severity was examined by illness characteristics such as duration of illness, number of depressive and (hypo)manic episodes, and impairment of psychosocial functioning (assessed with the Medical Outcomes Study 36-Item Short-Form Health Survey (MOS-SF-36), Ware & Sherbourne, 1992). Age of onset was younger, and, as a result, the mean duration of illness longer for the respondents with both a CIDI/DSM-III-R and SCID/DSM-IV diagnosis of bipolar spectrum disorder than for the respondents with only a CIDI/DSM-III-R but no SCID/DSM-IV diagnosis of bipolar spectrum disorder (24.8 years versus 30 years). These differences were not statistically significant, possibly due to low power. Respondents with a CIDI/DSM-III-R diagnosis of bipolar I disorder were not more often diagnosed with the SCID with a DSM-IV bipolar spectrum disorder compared to respondents with a CIDI/DSM-III-R diagnosis of bipolar disorder NOS. Number and type of comorbid SCID/DSM-IV diagnoses could not explain discrepancies between CIDI/DSM-III-R and SCID/DSM-IV diagnoses either.

Based on the CIDI, the number of symptoms ever experienced by the respondents during a (hypo)manic episode was not different between respondents with and without a SCID/DSM-IV diagnosis of bipolar spectrum disorder. However, based on the SCID, the mean number of (hypo)manic symptoms was significantly lower among the respondents with a CIDI /DSM-III-R diagnosis of bipolar disorder but no SCID/DSM-IV diagnosis of bipolar spectrum disorder, explaining the different SCID/DSM-IV diagnoses. However, respondents with a CIDI/DSM-III-R diagnosis of major depressive disorder and a SCID/DSM-IV diagnosis of bipolar spectrum disorder reported a mean number of CIDI (hypo)manic symptoms of 3 (50% of these respondents reported a distinct period with more activity observed by others without meeting the criteria for a DSM-III-R episode of (hypo)mania). This suggests that these cases are subthreshold (subsyndromal) according to the CIDI but do reach the threshold for a diagnosis of

bipolar spectrum disorder when assessed with the SCID. Underdiagnosis of bipolar disorder by the CIDI, when compared to the SCID, may be the result of different weighting of severity of the various symptoms.

Specific symptom profiles, such as euphoria, grandiosity and the ability to maintain energy without sleep, which predicted the clinical validity of a CIDI/DSM-III-R diagnosis bipolar disorder in another reappraisal study by Kessler et al. (1997), were not confirmed in our study. The most reported symptoms with the CIDI among the respondents with both a CIDI/DSM-III-R and SCID/DSM-IV diagnosis of bipolar spectrum disorder were distractibility (90%), inability to sit still (86.7%), and racing thoughts (83.3%). Grandiosity was reported by only 13.3% of the respondents. For the respondents with only a CIDI/DSM-III-R diagnosis of bipolar disorder but no SCID/DSM-IV diagnosis of bipolar spectrum disorder, the most reported symptoms were distractibility (95.5%), inability to sit still (79.5%) maintaining energy without sleep (81.8%) while grandiosity was reported by only 4.5% of the respondents.

We screened the respondents with the Personality Disorders Questionnaire (PDQ-4+, Hyler, 1994). The majority of the positive screens for personality disorders concerned the categories of paranoid, avoidant and obsessive compulsive disorders (see chapter 2, table 2.5). Overdiagnosis of bipolar disorder by the CIDI/DSM-III-R could not be explained by misdiagnosis of borderline personality disorder as bipolar disorder. However, one must realize that the PDQ-4+ is not a diagnostic instrument but merely a screening instrument with high sensitivity but only moderate specificity.

These findings of overdiagnosing and underdiagnosing bipolar disorder by the CIDI could suggest that a CIDI diagnosis may not necessarily correspond to a clinical diagnosis of bipolar disorder. However, in addition to the 40.5% with a SCID/DSM-IV bipolar spectrum disorder, 42 % of the respondents with a CIDI/DSM-III-R diagnosis of bipolar disorder had a SCID/DSM-IV diagnosis of major depressive disorder, so more than 82.5% of the respondents with a CIDI diagnosis of bipolar disorder still had a DSM-IV major mood disorder when diagnosed by the SCID. At least part of the discrepancy is likely to be explained by inconsistent reporting of episodes by respondents, which influences the comparability of the diagnostic assessments at different times (Mc Leod et al., 1990; Haro et al., 2006). It can be expected that some of the respondents with a CIDI/DSM-III-R diagnosis of bipolar disorder at any of the assessment points in NEMESIS did not recall the (hypo)manic episode during the SCID interview and vice versa, resulting in a change of type of mood disorder (depressive disorder versus bipolar disorder). In addition, the change of severity of psychopathology (e.g., subthreshold hypomania versus syndromal hypomania) occurring in the periods between the CIDI and SCID interviews may in part explain the discrepancies. Furthermore, the fully structured way a (hypo)manic episode is questioned in the CIDI with yes or no answers is in contrast with the flexible open-ended and conversational probing by clinicians

with the SCID (Haro et al., 2006). It can be assumed that especially for a valid diagnosis of a (hypo)manic episode with a structured interview performed by lay-interviewers, a more detailed assessment and weighing of the various (hypo)manic symptoms is necessary. In the most recent version of the CIDI (version 3.0, Kessler & Üstün, 2004), the symptoms of mania/hypomania are questioned in more detail and the severity of a symptom is also assessed instead of only assessing whether a symptom is present or not (which was the case in the CIDI version 1.1).

Indeed, this resulted in better agreement between diagnoses with fully structured and semi-structured interviews. Kessler et al. (2006*a*) assessed the validity of bipolar spectrum disorder based on the CIDI version 3.0 in the National Comorbidity Survey-Replication (NCS-R) using the SCID. Both instruments in this study resulted in DSM-IV diagnoses. Their reappraisal sample included 40 NCS-R respondents: 10 with a CIDI diagnosis of bipolar I disorder, 10 with a CIDI diagnosis of bipolar II disorder, 10 with a CIDI sub-threshold bipolar disorder and 10 with no bipolar spectrum disorder who endorsed a CIDI diagnostic stem question for mania/hypomania. The total prevalence estimate of DSM-IV bipolar I disorder, bipolar II disorder and subthreshold bipolar disorder based on the SCID was 4.0% compared to 4.4% with the CIDI. Concordance of CIDI and SCID diagnosis was excellent for any bipolar disorder with a κ of 0.94, a positive predictive value (percentage of CIDI cases confirmed using the SCID) of 0.88 and a negative predictive value (percentage of CIDI non cases confirmed as not being cases using the SCID) of 1.0. The concordance of CIDI-SCID diagnosis was considerably higher for bipolar I disorder (κ=0.88, PPV=0.79, NPV=1.0) than bipolar II disorder (κ 0.50, PPV=0.41, NPV=0.997) and subthreshold bipolar disorder (κ=0.51, PPV=0.58, NPV=0.990).

To conclude, the CIDI version 3.0 and the SCID will probably result in more valid diagnoses than the CIDI version 1.1 that was used in NEMESIS.

Societal cost and quality of life of respondents with a bipolar spectrum disorder in the general population

In the 40 respondents with a SCID/DSM-IV diagnosis of bipolar spectrum disorder, disorder-related societal cost and self-reported quality of life were measured. The 'Trimbos and iMTA questionnaire on Costs associated with Psychiatric illness' (TiC-P, Hakkaart-van Roijen, 2002) was used to collect data on direct and indirect costs generated by bipolar spectrum disorder. Direct costs were defined as costs due to medical consumption. The indirect costs were defined as the productivity loss due to absence from work and reduced efficiency at work. To assess the impairment of psychosocial functioning, we applied the Medical Outcomes Study 36-Item Short-Form

Health Survey (MOS-SF-36, Ware & Sherbourne, 1992) and the EuroQol: 5 Dimensions (EQ-5D, Essink-Bot et al., 1993). Self-perceived health status was assessed with the Visual Analogue Scale (VAS, van Roijen et al., 1996), the scores of which range from 0 (worst imaginable health state) to 100 (best imaginable health state).

The majority of the 40 respondents (N=30, 75%) had a paying job. Compared to the general population, respondents with a SCID diagnosis of bipolar spectrum disorder reported a higher number of days of absence from work (13 versus 55.5 days per year, *P*=0.007) and reduced efficiency at work (1.3 versus 7.7 days per year, NS), resulting in mean indirect costs of €3629 (US$3432)[1] per respondent with a paying job per year (chapter 3). This high number of days of absence from work is comparable to the results from the National Comorbidity Survey Replication in which a number of 65.5 lost workdays per employee with bipolar disorder was found (Kessler et al., 2006*b*). There were no significant differences in indirect costs between the various subtypes, indicating that the most severe type of bipolar disorder (bipolar I disorder) did not lead to more reduced efficiency and more days of absence than the less severe subtypes. However, this may also partly be explained by the fact that the indirect costs were based on respondents with a paying job and only 57% of the respondents with a bipolar I disorder had a paying job (compared to 85% of the respondents with bipolar II disorder and other bipolar disorder) (chapter 6). The total mean direct costs due to medical consumption were €897 (US$848) per respondent per year. Significantly more respondents with bipolar I disorder consulted a mental health care professional, used antipsychotics, received psychological treatment and day treatment or were hospitalized, resulting in a significantly higher amount of direct medical costs (€1539, US$1455) than respondents with bipolar II disorder (€423, US$400, *P*=0.004) and other bipolar disorder (€721, US$682, *P*=0.038) (overall *P*=0.012) (chapter 6). The total annual direct and indirect costs of bipolar spectrum disorder in the Netherlands based on the 5.2% prevalence were estimated at €1.94 billion (US$ 1.83 billion[2]). Seventy-five percent of the total costs were due to indirect costs, which is somewhat less than the figures from studies elsewhere in the world (Wyatt & Henter, 1995; Das Gupta & Guest, 2002).

In chapter 3 we also reported on the quality of life of respondents with a SCID/DSM-IV diagnosis of bipolar spectrum disorder. The respondents reported a lower, although not significantly so, quality of life, measured by using the EuroQol, in comparison to people in the general population (*P*=0.084). However, the mean score for self-perceived health status, measured by using the VAS, was significantly lower than the mean score in the general population (77.18 versus 84.2, *P*=0.013) (chapter 3).

1 the costs are converted from € to US$ based by the mean exchange rate for 2002 of 1€ = 0.9456 US$. The data on costs were collected in 2002

2 billion (*miljard* in Dutch): 1000 times a million

Bipolar disorder: categories or dimensions

Despite the low concordance between the CIDI and SCID diagnosis of bipolar disorder, we examined in chapters 4 and 5 the milder expressions of mood disorders among the NEMESIS respondents who reported lifetime mood symptoms assessed by the CIDI. Although the validity of a CIDI/DSM-III-R diagnosis of bipolar disorder towards a SCID/DSM-IV diagnosis of bipolar spectrum disorder appears to be low, the CIDI is a reliable instrument with high interrater and test-retest reliability (Wittchen, 1994). Therefore, the use of CIDI data on lifetime mood symptoms seems justified.

In chapter 4 we reported on the temporal relation between subthreshold and clinical expression of mood disorders expressed as predictive value and likelihood ratios (LR). At the first NEMESIS interview, the presence of any lifetime depressive or (hypo)manic symptom and the total number of lifetime depressive or (hypo)manic symptoms were assessed with the CIDI. The depressive symptom had to have been present for at least 2 weeks and the (hypo)manic symptom had to have been present for at least 2 days. At the second and third NEMESIS interviews, the presence of incident DSM-III-R major depression or incident bipolar disorder (bipolar I disorder and bipolar disorder NOS) was assessed, hereafter referred to as post-baseline major depression and post-baseline bipolar disorder, respectively.

The sample in this study consisted of all respondents who at baseline never had any diagnosis of major depression *nor* any diagnosis of bipolar disorder as well as all respondents who had had at least one post-baseline CIDI interview (T_1 or T_2). After applying these criteria, 4628 respondents were included. The prevalence of any number of lifetime depressive symptoms was 17.2% and of any lifetime (hypo)manic symptoms was 1.2%. The 3 years post-baseline incidence for major depression was 5.5% and for bipolar disorder 0.3%. We found a predictive value of lifetime depressive symptoms for post-baseline major depression of 13.6% (95% CI: 12.6-14.5) (LR 2.7; 95% CI: 2.3-3.2) and for post-baseline bipolar disorder of 1.0% (95% CI: 0.7-1.3) (LR 3.3; 95% CI: 2.1-5.3). We determined a predictive value of lifetime manic symptoms for post-baseline major depression of 17.9% (95% CI: 16.8-19.0) (LR 3.7; 95% CI: 1.9-7.3) and for post-baseline bipolar disorder of 7.1% (95% CI: 6.4-7.9) (LR 25.4; 95% CI: 10.6-60.6). These results show a high level of cross-prediction across mood symptoms. Moreover, (hypo)manic symptoms had higher predictive values and likelihood ratios than depressive symptoms not only for bipolar disorder but also for major depression. This suggests that experiencing (hypo)manic symptoms is a stronger indicator and more specific of vulnerability for mood disorders and affective dysregulation than depressive symptoms. In addition, the higher the number of lifetime mood symptoms at baseline, the higher the risk for incident mood disorder (bipolar disorder or major depression) during the three years of follow-up. Predictive values and likelihood ratios ranged from

14.3% to 50% and from 2.7 to 16.4, respectively (chapter 4, table 4.3 and 4.4). Thus, the predictive value of mood symptoms for developing mood disorder increased in a dose-response fashion with increasing numbers of symptoms.

Although we used a broad definition of subthreshold (hypo)mania, we found a lower rate of subthreshold (hypo)mania compared to the prevalence of up to 8.9% found in other studies (Judd & Akiskal 2003; Angst et al., 2003*a*). One explanation could be differences in the required duration of symptoms. In the study of Angst et al. (2003*a*), no minimum duration of (hypo)manic symptoms was required.

In chapter 5 we studied whether depressive and manic epsiodes independently influence help-seeking behaviour and need for care. If this is true, a higher level of comorbidity between manic and depressive episodes would be found in clinical samples compared to non-clinical samples. The association between both dimensions in clinical samples appears to be high due to the fact that both manic and depressive dimensions contribute to help-seeking behaviour and need for care. These independent effects of both dimensions on help-seeking will lead to an increase in the number of patients in clinical samples with mania-depression comorbidity (so-called Berkson's Bias). Consequently, manic and depressive dimensions are much more loosely associated with each other in the general population of non-help-seeking individuals.

We examined in the NEMESIS population whether manic and depressive dimensions independently contributed to the use of mental health service and determined the degree of comorbidity between manic and depressive dimensions in respondents with and without mental health service use. Dimensions of depression and mania were expressed dichotomously as present or absent in the case of two or more lifetime depressive and three or more lifetime manic symptoms assessed with the CIDI (hereafter depression-lifetime and mania-lifetime, respectively). For the prospective analyses, a dichotomous variable indicating three or more mania symptoms at baseline and/or T_1 and/or T_2 (hereafter mania-total) was constructed as well as a similar measure of two or more depression symptoms at baseline and/or T_1 and/or T_2 (hereafter depression-total).

Indeed, manic and depressive dimensions contributed independently to mental health service use (see chapter 5, table 5.2) although the depressive dimension was more strongly associated with mental health service use (OR 7.6; 95% CI: 6.7-8.7) than the manic dimension (OR 2.6; 95% CI: 2.0-3.4). In respondents with lifetime mental health service use, the rate of mania-lifetime given the presence of depression-lifetime was 16.7%, which was considerably higher than the rate among respondents without lifetime mental health service use (7.1%) (see chapter 5, table 5.3). The difference of 9.6% (95% CI: 6.8%-12.3%) for mania-lifetime given the presence of depression-lifetime between respondents with and without lifetime mental health service use was highly significant (z=6.82, *P*=0.000). In respondents with first-ever mental health

service use (i.e., incident mental health service use between baseline and T_1 and/or T_2 in those without lifetime mental health service use), the rate of mania-total given the presence of depression-total was 10.8%, which was considerably higher than the rate of mania-total given the presence of depression-total among respondents without first-ever mental health service use (6.6%). The difference of 4.2% (95% CI 0.8%-7.7%) for mania-total given the presence of depression-total between respondents with and without first ever mental health service use was again significant (z=2.39, *P*=0.017). These results indicate that the bipolar phenotype consists of manic and depressive dimensions that may be much more loosely associated than (Berkson) biased clinical observations suggest.

In both studies we took a dimensional approach of mood symptoms. In chapter 4 we found that subthreshold expressions of depression and (hypo)mania are prevalent and continuous over time with more severe clinical states, which support a continuum from normal to pathological. In addition, we found cross-prediction of mood symptoms for developing a mood disorder, which supports a continuum from depressive to (hypo)manic states. These results are in line with a proposed model by Angst (2007) that unifies a categorical classification with a dimensional view. This model includes a severity spectrum ranging from psychotic major mood disorders to no symptoms (supernormal) and a proportionality mood spectrum from depression to mania. The concept of a mood spectrum is supported by the occurrence of mixed episodes with symptoms of opposite polarity in the same episode. A recent study among 441 treated individuals with bipolar disorder showed occurrence of clinically significant depressive symptoms (two or more symptoms) in 94.1 % of those with mania or hypomania; similarly, 70.1% of those in a depressive episode had clinically significant manic symptoms (Bauer et al., 2005). In another study among 908 treated individuals, it was found that in 57% of the cases hypomania co-occurs with depressive symptoms (Suppes et al., 2005*a*). In addition, Cassano et al. (2004) found a linear relationship between lifetime depressive and lifetime manic symptoms in patients with unipolar and bipolar disorder.

Familial data also support the idea of a mood spectrum. First-degree relatives of bipolar probands are not only at increased risk of bipolar disorder but also of unipolar major depression when compared with first degree relatives of controls (absolute risk is 8-20%, relative risk is doubled). Bipolar II disorder also occurs with increased frequency in relatives of bipolar I probands compared to the general population (Craddock & Jones, 1999). The familial aggregation of depressive disorder and bipolar disorder suggests a genetic overlap between both disorders. In addition, several studies showed that the diagnostic stability of major depressive disorder is low. In a 15-year follow-up study, 27% of the patients (N=74) hospitalized for unipolar major depression eventually developed

one or more hypomanic episodes while 19% developed one or more manic episode (Goldberg et al., 2001). Angst et al. (2005) found a conversion rate from depression to bipolar I disorder of 1% per year and to bipolar II disorder of 0.5% year. Across the entire lifetime, every new episode of depression brings a new risk for mania.

The spectrum of severity is supported by two prospective studies on the long-term course of symptoms in patients with bipolar I disorder or bipolar II disorder. Levels of severity of (hypo)manic symptoms and depressive symptoms fluctuated over time within the same patient (Judd et al., 2002, Judd et al., 2003).

We also found that manic and depressive dimensions may be more loosely associated than clinical observations suggest (chapter 5). These findings are in line with the two-illness model proposed by Joffe et al. (1999) that bipolar disorder constitutes two separate but related disorders, depression and mania. This model is supported by the fact that mania and depression are syndromes not specific to bipolar disorder but also arise in a variety of neuromedical and toxicological conditions (Baldessarini, 2000; Swann, 1999), for instance, mania during the use of corticosteroids, withdrawal or use of drugs and encephalitis (Krauthammer & Klerman, 1978) and depression as a comorbid disorder in other psychiatric disorders, chronic somatic conditions or as a result of the use or withdrawal of drugs or medication. Schweitzer et al. (2005) argued that bipolar disorder is more appropriately viewed as a manic disorder with or without comorbid depression because the syndrome of mania is the central distinguishing feature of bipolar disorder and most psychiatric disorders are commonly complicated by co-morbid depression.

Moreover, the differential response to lithium and lamotrigine are in favour of two distinct disorders. Lithium is likely to be more effective against mania than depression (Geddes et al., 2004), but among depressed patients it is also more effective in patients with prior (hypo)manic episodes (bipolar depression) than unipolar depression (Goodwin et al., 1972). Lamotrigine is more effective against depression than mania and also more effective for bipolar depression than unipolar depression (Vieta, 2004).

Recent genetic research supports the concept of symptom dimensions. The same genes are involved across the different diagnostic categories, i.e., major depressive disorder and bipolar disorder and even schizophrenia. For example, several studies investigated the involvement of variations at the Brain-Derived Neurotrophic Factor (BDNF) gene locus in major depressive disorder, bipolar disorder and schizophrenia. Two studies showed a positive association of BDNF with bipolar disorder (Skar et al., 2002; Neves Pereira et al., 2002), although negative results also have been reported (Nakata et al., 2003). Another study showed that BDNF is involved in unipolar depression (Ivy et al., 2003). The results of another study among individuals with major depressive disorder, bipolar disorder, schizophrenia and healthy controls suggest that BDNF may

be a susceptibility gene for major depressive disorder and for a subgroup of patients with schizophrenia, i.e., those with lifetime depressive symptoms (Schumacher et al., 2005). A twin study by McGuffin et al. (2003) found that although there is a substantial genetic correlation between mania and depression, specific genes contribute to the manic state. These studies support the possibility of relatively specific relationships between genotype and symptom-dimensions.

Our finding of relatively separate manic and depressive dimensions seems to contrast with the concept of a mood spectrum. However, pure mania and pure depression can be seen as the two extremes of one mood spectrum. Mood disorders can be conceptualised as a disease with affective dysregluation as a core feature. The clinical expression of affective dysregulation varies on a continuum from pure depressive to pure manic symptoms with different mixed states (depression with manic symptoms or mania with depressive symptoms) in between. In addition, the severity of manic and depressive symptoms varies on a continuum from normal to pathological.

Implications for DMS-V

In the current categorical system of the DMS-IV, boundaries between the various diagnostic categories are arbitrarily set and do not represent nature. Depression and mania (as well as psychosis) are better considered on a continuum. The same is true for the boundaries between illnesses/categories and normality. In addition, illness characteristic such as episode frequency should also be seen as a dimension instead of a categorical course specifier. A study by Kupka et al. (2005) in 539 outpatients with bipolar disorder showed that a rapid cycling course as defined in de DSM-IV is not a distinct subtype of bipolar disorder but is arbitrarily defined on the continuum of episode frequency. A combination of a categorical and dimensional system as proposed by Angst (2007) would be useful for clinical practice and the DSM-V. Although a categorical approach conforms to the way clinicians think, a dimensional approach is closer to reality. Psychopathology could be described along a number of dimensions, for example high on depression, high on mania, low on psychosis and high on episode frequency (First, 2002).

Goodwin and Jamison (2007) proposed the following organization of mood disorders: a division in recurrent (episodic) affective disorders (Kraepelin's manic-depressive illness) and depressive disorders. Recurrent affective disorders are subdivided into bipolar disorder (ranging from bipolar I disorder to cyclothymia) and unipolar disorder (psychotic and non-psychotic). Depressive disorders include major depression (psychotic and non-psychotic), dysthymia and depressive disorder NOS. They emphasize the importance of recurrence or cycling as a distinguishing feature

in mood disorders rather than the occurrence of a manic pole and thus a return to the original Kraepelinian concept of manic-depressive illness (Katzkow et al., 2003; Goodwin & Jamison, 2007).

Recognition and treatment of bipolar spectrum disorder in the general population

In our reappraisal sample of 40 respondents with a SCID/DSM-IV bipolar spectrum disorder, we investigated the degree of recognition and treatment. In addition we identified factors influencing recognition and treatment.

In general, several factors contribute to the recognition of a disease. The first include factors inherent to the illness such as the perceived better functioning in a hypomanic episode (Judd et al., 2005) with as a consequence hypomanic symptoms not being mentioned spontaneously or not recognized by the doctor as abnormal. Another example is a state dependent memory distortion, i.e., difficulty remembering (hypo)manic episodes during a depressive state. The second include factors related to the patient, such as help-seeking behaviour and knowledge about the disorder. The third include factors related to health care professionals, e.g., whether they are sufficiently trained to recognize this specific disorder.

The results of our study show that these factors all contribute to the recognition of bipolar disorder (chapter 6). Most of the respondents with a SCID/DSM-IV bipolar spectrum disorder sought help for depression and did not perceive their hypomanic episodes as something abnormal. Although almost all respondents consulted a health professional, only 12.5% (N=5) of the respondents reported that they had received a diagnosis of bipolar disorder and agreed with the diagnosis. Only these respondents used a mood stabilizer and had frequent contact with a psychiatrist or psychologist (see case description number one). Thus, self-awareness of bipolar disorder appears to be an important factor in receiving adequate treatment. As illustrated by two out of three case descriptions of study respondents, it can be assumed that bipolar disorder is not adequately recognized by general practitioners and mental health professionals. In the first case the respondent received the diagnosis of bipolar disorder with a delay of several years. In the second case the respondent never received a diagnosis of bipolar disorder despite there being a need for treatment. Although the respondent in the last case fulfilled the criteria for bipolar disorder, the need for treatment in this case can be questioned as there was no impairment of functioning .

Since our data on previously received diagnosis and treatment were based on report of the respondents and were not verified with their health care professionals, the true percentage of underrecognition may be lower than our study suggests.

Possibly some of the respondents had received the diagnosis of bipolar disorder but had forgotten it or denied the diagnosis. Nevertheless, this stresses the importance of self-recognition of bipolar disorder in receiving adequate treatment. Surprisingly, comorbidity and severity of bipolar disorder, expressed by type of bipolar disorder, number of episodes and age of onset did not influence recognition.

A survey of the US population completed by the Depression and Bipolar Alliance showed that nearly half of the respondents had never heard of bipolar disorder or manic depression (Lewis, 2003). Recently, a survey among 500 US and UK psychiatrists was performed to identifying barriers and unmet needs in the management of patients with bipolar disorder. They reported that the most important needs included education and support for patients and families, education of general practitioners to improve earlier recognition and referral to specialist care and education of the general public to improve awareness and understanding (Chengappa & Williams, 2005). Better education of the general public regarding the symptoms and consequences of bipolar disorder could motivate patients to seek help and improve recognition (Bhugra & Flick, 2005).

Case presentations:

1. Recognized diagnosis of bipolar disorder and receiving adequate treatment

Mr. A. (age 35 years) fulfilled the criteria for a DSM-IV diagnosis bipolar II disorder and a mood disorder (manic episodes and rapid cycling pattern) induced by the use of antidepressant. In addition he had a comorbid panic disorder with agoraphobia and social phobia.

He experienced the first depressive symptoms when he was 15 years old. When he was 22 years, he developed a seasonal pattern: in spring and autumn he had a major depressive episode, and in summer he had hypomanic episode. He explained these hypomanic episodes as a compensation of the depressive episodes and was happy to get out of his bed. At the age of 29, he consulted his general practitioner for a depressive episode and panic attacks with agoraphobia and social phobia. He received an antidepressant, sedative, and psychotherapy. Subsequently, his mood began to cycle with manic episodes that lasted for 2-3 weeks followed by a period of 1-2 weeks in which he felt exhausted and depressed. When he was 32 years old, he consulted a psychiatrist and was diagnosed with a bipolar disorder. The antidepressant was stopped, lithium was started, and he received psychoeducation. Since then, his mood has stabilized and the comorbid panic disorder has also come into remission.

2. Unrecognized diagnosis of bipolar disorder but need for treatment

Mr B. (age 32 years) was diagnosed with a DSM-IV diagnosis of bipolar I disorder. He started suffering from recurrent depressive episodes from the age of 16. When he was 24 and 26 years old, he experienced a manic episode. During the last episode, he initially felt very good with inflated self-esteem; he needed less sleep, and he had lots of plans and ideas. On his job, he had conflicts with co-workers, and as a result, he was sent home. The general practitioner started antidepressants and referred him to a psychotherapist. He got more confused and did impulsive, strange things. He went on a survival expedition in the woods, slept in huts and slept in a hotel without carrying money. Finally, he panicked. When he got back home, he consulted a mental health care professional and was diagnosed as psychotic. The antidepressant was stopped, and an antipsychotic was prescribed. Initially, they thought he was suffering from bipolar disorder or psychotic disorder. After three months, he was referred back to the psychotherapist.

3. Diagnosis of bipolar disorder but no need for treatment

Mr C. (age 52 years) was diagnosed with a DSM-IV bipolar II disorder. He works as a graphic designer and is married. Once in his life, at the age of 35 years, he experienced a depressive episode with a sad mood, loss of interest, problems with concentration, hypersomnia, loss of energy and fatigue, which lasted for 6 weeks. About 10 years later, he experienced the first hypomanic episode with elevated mood and more energy lasting 3 weeks. He needed less sleep, had many creative ideas, was more talkative and more productive in his job. Since then he has experienced such episodes three times a year mostly starting when there are deadlines at his job. He likes these periods, and he experiences them as useful for his job. He regrets it when such a period is over. His wife and colleagues do notice a change of mood and activity. According to them he is hyperactive, talkative and has an elated mood. He only visited the general practitioner in his depressive episode, and he has never received treatment. Although he clearly experiences hypomanic episodes, there seems to be no need for treatment. There is no impairment in functioning; actually he functions better, and up to the time of the interview, no recurrence of the depressive period occurred.

Strengths and limitations of the study

Our study has several strengths:

1. NEMESIS is the first study in the Netherlands on the prevalence of psychiatric disorders in a representative sample of the Dutch population.
2. A major strength of NEMESIS is its longitudinal designs, which made it possible to study the development of mood disorders over time (chapter 4).
3. Thanks to the detailed assessment by the CIDI of all DSM-IV depressive and manic/hypomanic symptoms, we could study the milder expressions of bipolar disorder (chapter 5). In combination with the longitudinal design, it was possible to examine the transition rates of these milder (subthreshold) expressions to a clinical disorder (chapter 4).
4. In the reappraisal study that forms the basis of chapters 2, 3 and 6 of this thesis, diagnoses were based on a clinical interview (SCID) performed by trained and experienced clinicians, and a history of diagnosis and treatment was asked about in detail by the same clinicians in a sample recruited from the general population. This gave us the unique opportunity to identify and study general population subjects, who were previously given another diagnosis or who had never sought help, with a diagnosis of bipolar spectrum disorder that was confirmed by clinicians. Other studies in the general population on recognition and treatment rates used self-reported screening questionnaires (MDQ) or highly structured interviews (such as the CIDI) performed by trained lay interviewers and asked only globally about prior diagnostics and treatment. Alternatively, research done in clinical samples is biased by help-seeking behaviour.

The study also has several limitations

1. People with no fixed address and those who remain institutionalized for long periods were not included in the original NEMESIS study. It is likely that especially among homeless and institutionalized people relatively high prevalences of mental illnesses will be found. However, due to the low numbers of homeless people in the Netherlands, the influence on prevalence rates will be small. Moreover, exclusion of the institutionalized people kept the sample free from a help-seeking bias.
2. Only respondents who speak fluent Dutch were included, and therefore, the sample probably missed the first generation groups of immigrants (in 1996, the first assessment point of NEMESIS, 8.3% of the Dutch population were immigrants (CBS)).

3. The three-year incidence of bipolar disorder in NEMESIS of 0.3 is relatively high in relationship to a lifetime prevalence of 1.9. This can be explained by the design of the study. Respondents were classified as having bipolar disorder when they were recognized as such at one of the three assessment points. During the subsequent CIDI interviews, a diagnosis of major depressive disorder could switch to bipolar disorder but not vice versa. Therefore, the lifetime prevalence of bipolar disorder could only increase over the three assessment points of NEMESIS. It is clear that conversion from unipolar to bipolar disorder is in reality not a new case; therefore, the true incidence rate is lower than suggested by these numbers.
4. The lifetime diagnosis of bipolar spectrum disorder, both with the CIDI in NEMESIS and with the SCID in the reappraisal study, was based on retrospective recall. This approach can be problematic in recording lifetime symptoms and disorders due to difficulties in accurate recall. The more severe symptoms and episodes that led to impairment and treatment seeking are more likely to be remembered than milder episodes. Therefore, underestimation of the prevalence of bipolar (spectrum) disorder could have occurred.
5. Related to this recall bias is the fact that no significant others were interviewed, and a diagnosis of bipolar disorder was only based on a self-report of mood episodes. Hypomanic episodes are often experienced as ego-syntonic while family and significant others generally provide more reliable reports (Angst et al., 2003*a*; Akiskal, 2002). This may also have contributed to underestimation of bipolar II disorder and bipolar disorder NOS.
6. Only about half (46.8%) of all NEMESIS respondents with a CIDI diagnosis of bipolar disorder participated in the reappraisal study, which is inevitable when respondents are recruited from the general population.

Implications of our study for clinical practice

1. In our study we found a prevalence of DSM-IV bipolar spectrum disorder of 5.2% and low rates of recognition and treatment. It can be questioned whether the milder expressions of bipolar disorder need treatment. A diagnosis of bipolar spectrum disorder does not necessarily imply a need for treatment, as is illustrated by the third case description. There was no clear need for treatment in this case as there was no impairment of functioning or distress. The respondent even reported better functioning. Still, there may be a risk of further worsening of the illness. A recent study by Kessing et al. (2004) among respondents of the Zurich study showed that in depressive

and bipolar disorder, the risk of subsequent recurrences increases with the number of episodes. This is congruent with the kindling hypothesis, which poses that the first episodes of full mania or depression are often precipitated by episodes with milder symptoms, i.e., hypomanic or minor depressive episodes. In addition, every new episode leaves traces and contributes to the vulnerability of further occurrences of mood episodes (Post 1992; Post et al., 1986). These findings stress the importance of early detection, intervention and prophylactic treatment to enhance long-term outcome and prevent the deterioration (social and vocational) of functioning. In addition, it is important to recognize subthreshold depression and mania because, as our results show, these less severe expressions of mood disorders are a risk factor for developing a major depressive disorder or bipolar disorder (chapter 4) and may also lead to psychosocial impairment and decrease of quality of life (chapter 3). For the above case description, this implies that a close follow-up is indicated and that he should be advised to consult a health professional if future episodes cause distress or impairment in functioning.

2. In our reappraisal study, about half of the respondents with a SCID/DSM-IV bipolar spectrum disorder reported that their illness had started with a depressive episode or with depressive symptoms and most respondents had sought treatment for depressive mood and anxiety. However, the onset with depression may be even higher than the results of our retrospective study indicates. In a prospective study among children aged 16-26 years of parents with bipolar disorder, almost all the children with bipolar disorder (92%) debuted with a depressive mood disorder (Hillegers et al., 2005). Probably because overactivity, euphoria or irritability were not thought of as pathological symptoms and were often experienced as ego-syntonic, most respondents did not consult a mental health care professional for these symptoms. Therefore, general practitioners and mental health care professionals should always consider bipolar spectrum disorder and ask about a history of (hypo)mania in patients presenting depression or anxiety. Indicators of bipolarity in patients presenting depression are early age of onset (< age 25), atypical depressive features, brief major depressive disorder (on average < 3 months), rapid on/off pattern, seasonality, more than three major depressive episodes, psychotic symptoms, postpartum depression, wearing off of antidepressant efficacy, lack of response to three or more antidepressant treatment trials, hyperthymic personality at baseline or a family history of bipolar disorder (Ghaemi et al., 2002; Berk & Dodd, 2005; Kaye, 2005; Suppes et al., 2005; Perlis et al., 2006). Increased goal-directed activity and higher energy levels are frequently reported hypomanic symptoms (Angst et al., 2003*b*; Benazzi and Akiskal, 2003) and appear to be a sensitive marker of bipolar II disorder (Benazzi, 2003).

3. A screening instrument such as the Mood Disorder Questionnaire (MDQ, Hirschfeld et al., 2003) or the hypomania checklist (HCL-32, Angst et al., 2005) could be helpful in detecting bipolar disorder in patients with depression. In addition, the Bipolarity Index, developed by Sachs et al. (2004), may be helpful. Unlike a DSM-IV based diagnostic system, which emphasizes separate diagnostic categories, the Bipolarity Index places patients on a spectrum and emphasizes diagnostic features other than hypomania. The following five dimensions of bipolarity are considered: characteristics of (hypo)mania, the age of onset of the first mood symptoms, illness course and other features (such as substance use, legal problems associated with mania, features of borderline personality disorder and anxiety disorder, ADHD as a child, hyperthymic temperament), response to medication and family history. All dimensions receive equal weight although this still needs to be validated. Another dimensional instrument to diagnose bipolar disorder is the Bipolar Affective Disorder Dimension Scale, developed by Craddock et al. (2004), that assesses the dimensions of mania, depression, psychotic features, and mood incongruence.
4. Our reappraisal study showed that self-recognition appears to be the most important factor in treatment seeking and receiving adequate treatment. This stresses the importance of paying attention to acceptance when the diagnosis of bipolar disorder is made. Studies have shown positive effects of psycho-education and psychological treatment (i.e., cognitive behavioural therapy, interpersonal social rhythm therapy and family-focused therapy) on the acceptance of the diagnosis and medication adherence (Perry et al., 1999; Colom et al., 2003; Lam et al., 2003; Miklowitz et al., 2003; Frank et al., 2005; Miklowitz, 2006). Although these forms of psychotherapy have different foci, they all involve education about bipolar disorder, thereby fostering insight into the illness and the need for medication. In addition, retrospective and prospective mood charting could be helpful in improving insight into the illness and adherence to therapy (Baldassano, 2005). Kay Redfield Jamison described the need for a combination of medication and psychotherapy as follows:

   No pill can help me deal with the problem of not wanting to take pills, likewise no amount of analysis alone can prevent my manias and depressions.

   (Cited from: *An unquiet mind; a memoir of moods and madness* by Kay Redfield Jamison 1995)

Implications of our study for further research

1. A categorical model, such as the DSM-IV, is indispensable for clinicians to speak the same language and develop treatment modalities. However, it is important to notice that diagnostic categories based solely on clinical description are merely artificial constructions and that these diagnoses and the boundaries between diagnostic categories do not represent nature per se. Our studies support the idea that dimensions represent nature better than categories. Historically, unipolar disorder, bipolar disorder and schizophrenia were lumped together or divided into different diagnostic categories. Until now the division into different diagnostic categories have not helped to clarify the aetiology of these disorders. In contrast, genetic research in the last few years gives evidence of a continuum between the various diagnostic categories. Some syndromes and symptom dimensions may share the same genes, and some genes may be specific for a symptom dimension (Cardno et al., 2001; Kendell & Jablensky 2003). Mood disorders (bipolar disorder and recurrent depressive disorder) can be conceptualized as a disorder with as a core feature affective dysregulation. Specific genes will predispose an individual to affective dysregulation, and in combination with environmental factors and additional genes for mania or additional genes for depression, an individual will develop a pure depression or pure mania or a mixture, depending on the effect size of the several genes. Therefore, it may be rewarding to identify separate risk factors for manic and depressive dimensions in addition to risk factors for affective dysregulation. Other dimensions of a bipolar phenotype for future research to clarify the pathophysiology can be psychosis, cyclicity, episode frequency, cognitive problems and comorbidity.
2. We found that subthreshold expressions of depression and (hypo)mania are continuous with the more severe clinical states and are a risk factor for developing a future major depressive disorder or bipolar disorder. The theoretical implications of the findings are that mood symptoms can be seen as intermediary phenotypes of a mood continuum that after exposure to additional risk factors may progress to a full-blown disorder (Hanssen et al., 2003). Additional risk factors may be stressful life events or a positive family history for mood disorders (van Os et al., 2001). Hillegers et al. (2004) showed that in addition to a family history of mood disorders, life events do increase the risk of developing a mood disorder in children of patients with bipolar disorder. This is in line with the findings of de Graaf et al. (2002) that negative life events and "ongoing difficulties" are predictors of mood disorders. It has been reported that the personality features characterised by"frequent ups and

downs" and the tendency to experience negative emotions (neuroticism) are risk factors for mood disorders (van Os & Jones 1999; de Graaf et al., 2002; Angst et al., 2003*b*). Johns and van Os (2001) hypothesised that psychological factors, such as dysfunctional attributions or coping styles, might be important in the transition from a subthreshold syndrome to a clinical disorder characterised by a need for care.

3. Further research to identify the factors that contribute to the transition from a subthreshold syndrome to a clinical disorder is useful in the prevention of mood disorder and is likely to clarify the aetiology of mood disorders.

Final conclusion

In our study among respondents from the general population with a CIDI/DSM-III-R diagnosis of bipolar disorder or major depressive disorder, we found a low concordance between a CIDI and a SCID diagnosis. This is probably best explained by the structured way (hypo)manic symptoms are explored (in the CIDI with yes or no questions in contrast to the open-ended and conversational probing with the SCID), inconsistent reporting of episodes by respondents (which influences the comparability of the diagnostic assessments at different times) and the change of severity of psychopathology (e.g., subthreshold hypomania versus syndromal hypomania) occurring in the period between the CIDI and SCID interviews.

Based on the SCID, we found a prevalence of 5.2% of DSM-IV bipolar spectrum disorder. Despite the fact that these respondents reported impaired functioning and a lower quality of life, recognition of bipolar spectrum disorder by general practitioners and mental health care professionals was low. Although obviously not all respondents with a bipolar spectrum disorder needed treatment at the time of the interview, better detection and follow-up of respondents with milder expressions of bipolar disorder is important because these less severe expressions are a risk factor for developing episodes of full mania or depression.

Our study shows that self-recognition is the most important factor in treatment seeking and receiving adequate treatment. Therefore, it is important to pay attention to awareness and acceptance of the disorder when the diagnosis of bipolar disorder is made.

Our results support the idea of a continuum from depressive to manic states with pure mania and pure depression as the two extremes of a mood spectrum as well as a continuum from normal to pathological. We conclude that a dimensional approach of symptoms represent nature better than a categorical one. Therefore, a combination of a categorical and a dimensional system would be useful for clinical practice. Although

a categorical approach reflects the way clinicians think, a dimensional approach is closer to reality. Psychopathology could be described along a number of dimensions, for example high on depression, high on mania, low on psychosis and high on episode frequency.

Mood disorders can be conceptualised as disorders with affective dysregulation as a core feature. To clarify the complex aetiology of mood disorder, it may be rewarding to identify separate risk factors for manic and depressive dimensions in addition to risk factors for affective dysregulation.

References

Akiskal HS. Classification, diagnosis and boundaries of bipolar disorder. In: Maj M, Akiskal HS, Lopez-Ibor JJ, Satorius N (eds.), Bipolar Disorder, Wiley, London, 2002.

Angst J, Gamma A, Benazzi F, Adjacic V, Eich D, Rössler W. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J Affect Disord 2003*a*;73:133-146.

Angst J, Gamma A, Endrass J. Risk factors for the bipolar and depression spectra, Acta Psychiatr Scand, 2003*b*;108 (Suppl. 418): 15-19.

Angst J. Sellaro R, Stassen HH, Gamma A. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. Journal of Affective Disorders 2005*a*;84:149-157.

Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD, Skeppar P, Vieta E, Scott J. The HCL-32: Towards a self-assessment tool for hypomanic symptoms in outpatients. J Affect Disord 2005*b*;88:217-233

Angst J. The bipolar spectrum. Br J Psychiatry:2007: 190: 189-191.

Baldassano CF. Assessment tools for screening and monitoring bipolar disorder. Bipolar Disord 2005; 7(Suppl. 1): 8-15.

Baldessarini RJ. A plea for integrity of the bipolar disorder concept. Bipolar Disord 2000;2:3-7.

Benazzi F, Akiskal H. Refining the evaluation of bipolar II: beyond the strict SCID-CV guideline for hypomania. J Affect Disord 2003;73:33-38.

Benazzi F. Diagnosis of bipolar Ⅱ disorder: a comparison of structured versus semistructured interviews. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:985-991.

Berk M, Dodd S. Bipolar II disorder: a review. Bipolar Disord 2005;7:11-21.

Bhugra D, Flick GR. Pathways to care for patients with bipolar disorder. Bipolar Disord 2005;7:236-245.

Bauer MS, Simon GE, Ludman E, Unützer J (2005) 'Bipolarity' in bipolar disorder: distribution of manic and depressive symptoms in a treated population. Br J Psychiatry 187:87-88.

Cassano GB, Rucci P, Frank E, Fagiolini A, Dell'Osso L, Shear MK, Kupfer DF. The Mood Spectrum in Unipolar and Bipolar Disorder: Arguments for a Unitary Approach. Am J Psychiatry 2004;161:1264-1269.

Cardno AG, Sham PC, Murray RM, McGuffin P. Twin study of symptom dimensions in psychoses. Br J Psychiatry 2001;179:39-45.

CBS. http://statline.cbs.nl. In: Central Bureau for Statistics, 2007 (accessed on 13 June 2007).

Chengappa KNR, Williams P. barriers to the effective management of bipolar disorder: a survey of psychiatrist based on the UK and USA. Bipolar Disord 2005;7(Suppl. 1):38-42.

Colom F, Vieta E, Martinez-Aran A, Reinares M, Goikolea JM, Benabarre A, Torrent C, Comes M, Corbella B, Parramon G, Corominas J. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Arch Gen Psychiatry 2003;60:402-407.

Craddock N, Jones I. Genetics of bipolar disorder. J Med Genet 1999;36:585-594.

Craddock N, Jones I, Kirov G, Jones L. The Bipolar Affective Disorder Dimension Scale (BADDS) - a dimensional scale for rating lifetime psychopathology in bipolar spectrum disorders. BMC Psychiatry 2004;4:19.

Das Gupta R, Guest JF. Annual cost of bipolar disorder to UK society. Br J Psychiatry 2002;180:227-33.

Essink-Bot ML, Stouthard ME, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQolc-questionnaire. Health Econ 1993;2:237-46.

Faravelli C, Rosi S, Alessandra Scarpato M, Lampronti L, Amedei SG, Rana N. Threshold and subthreshold bipolar disorders in the Sesto Fiorentino Study. J Affect Disord. 2006;94:111-119.

First MB. A Research Agenda for DSM-V: Summary of the DSM-V Preplanning White Papers Published in May 2002. American Psychiatric Publishing Inc. http://dsm5.org/whitepapers.cfm (accessed on 9 February 2007).

Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagiolini AM, Grochocinski V, Houck P, Scott J, Thompsom W, Monk T. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Arch Gen Psychiatry 2005;62:996-1004.

Graaf R de, Bijl RV, Ravelli A, Smit F, Vollebergh WAM. Predictors of first incidence of DMS-III-R psychiatric disorders in the general population: findings from the Netherlands Mental Health and Incidence Study. Acta Psychiatr Scand 2002;106:303-313.

Geddes JR. Burgess S. Hawton K. Jamison K. Goodwin GM. Long-Term Lithium Therapy for Bipolar Disorder: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Am J Psychiatry 2004;161:217-222.

Ghaemi SN, Ko JY, Goodwin FK. " Cade's Disease" and Beyond: Misdiagnosis, Antidepressant Use, and a Proposed Definition for Bipolar Spectrum Disorder. W Can J Psychiatry 2002;47:125-134.

Goldberg JF, Harrow M, Whiteside JE. Risk for Bipolar Illness in Patients Initially Hospitalized for Unipolar Depression. Am J Psychiatry 2001;158:1265-1270.

Goodwin FK, Murphy DL, Dunner DL, Bunney WE Jr. Lithium response in unipolar versus bipolar depression. Am J Psychiatry 1972;129:44-47.

Goodwin FK, Jamison KR, Manic-depressive illness. Bipolar Disorder and Recurrent Depression, second edition, Oxford University Press, New York 2007.

Hakkaart- van Roijen L. Manual Trimbos/iMTA questionnaire for costs associated with psychiatric illness (in Dutch). Rotterdam: institute for Medical Technology Assessment, 2002.

Hanssen MSS, Bijl RV, Vollebergh W, van Os J. Self-reported psychotic experiences in the general population: a valid screening tool for DSM-III-R psychotic disorders?. Acta Psychiatr Scand 2002;107:369-377.

Haro JM, Arbabzadeh-Bouchez S, Brugha TS, de Girolamo G, Guyer ME, Jin R, Lepine JP, Mazzi F, Reness B, Vilagut G, Sampson NA, Kessler RC. Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health Surveys. Int J of Methods in Psychiatr Res 2006;15:167-180.

Hillegers MHJ, Burger H, Wals, M. Reichart CG, Verhulst FC, Nolen WA, Ormel J. Impact of stressful life events, familial loading and their interaction on the onset of mood disorders; study in a high risk cohort of adolescent offspring of parents with bipolar disorder. Br J Psychiatry 2004:185:97-101.

Hillegers MHJ, Reichart CG, Wals M, Verhulst FC, Ormel J, Nolen WA. Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. Bipolar Disord 2005;7:344-350.

Hirschfeld RM, Holzer C, Calabrese JR, Weissman M, Reed M, Davies M, Frye MA, Keck P, McElroy S, Lewis L, Tierce J, Wagner KD, Hazard E. Validity of the Mood Disorder Questionnaire: A General Population Study. Am J Psychiatry 2003;160:178-180.

Hyler SE. Personality Diagnostic Questionnaire–4+ (PDQ-4+). New York State Psychiatric Institute, New York, 1994.

Ivy AS, Rodriquez FG, Garcia C, Chen MJ, Russo-Neustadt AA. Noradrenergic and serotonergic blockade inhibits BDNF mRNA activation following exercise and antidepressant. Pharmacol Biochem Behav 2003;75:81-88.

Jamison, K.R., An unquiet mind. Alfred A. Knopf, New York 1995. In het Nederland vertaald als: De onrustige geest. Luitingh-Sijthoff, Amsterdam 1996.

Joffe TR, Young LT, MacQueen GM. A two-illness model of bipolar disorder. Bipolar Disord 1999;1:25-30.

Johns LC, van Os J. The continuity of psychotic experiences in the general population. Clinical Psychology Review 2001;21:1125-1141.

Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB. The Long-term Natural History of the Weekly Symptomatic Status of Bipolar I Disorder. Arch Gen Psychiatry 2002;59:530-537.

Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser J, Solomon DA, Leon AC, Keller MB. A Prospective Investigation of the Natural History of the Long-term Weekly Symptomatic Status of Bipolar II Disorder. Arch Gen Psychiatry 2003;60:261-269.

Judd LL, Akiskal SA. The prevalence and disability of bipolar disorder spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. J Affect Disord 2003;73:123-131.

Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, Coryell W, Maser J, Keller MB. Psychosocial Disability in the Course of Bipolar I and II Disorders. Arch Gen Psychiatry 2005;62:1322-1330.

Katzkow JJ, Hsu DJ, Ghaemi SN. The bipolar spectrum: a clinical perspective. Bipolar Disord 2003;5:436-442.

Kaye NS. Is your depressed patient bipolar? J Am Board Fam Pract 2005;18:271-281.

Kendell R, Jablensky A. Distinguishing Between the Validity and Utility of Psychiatric Diagnoses. Am J Psychiatry 2003;160:4-12

Kessing LV, Hansen MG, Andersen PK, Angst J. The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders - a life-long perspective. Acta Psychiatr Scand 2004;109:339-44.

Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med 1997;27:1079-1089.

Kessler R C, Wittchen HU, Abelson MA, McGonagle K, Schwarz N, Kendler KS, Knäuper B, Zhao S. Methodological studies of the Composite International Diagnostic Interview (CIDI) in the US National Comorbidity Survey (NCS). Int J of Methods in Psychiatr Res 1998;7:33-55.

Kessler RC, Üstün TB. The World Mental Health (WMH) survey initiative version of the World Organization (WHO) Composite International Diagnostic Interview (CIDI) Int J Methods Psychiatric Res 2004:13;93-121.

Kessler RC, Akiskal HS, Angst J, Guyer M, Hirschfeld RMA, Merikangas KR, Stang PE. Validity of the assessment of bipolar spectrum disorders in the WHO CIDI 3.0. J Affect Disord 2006*a*;96:259-269.

Kessler RC, Akiskal HS, Ames M, Birnbaum H, Greenberg P, Hirschfeld RMA, Jin R, Merikangas KR, Simon GE, Wang PS. Prevalence and Effects of Mood Disorder on Work Performance in a Nationally Representative Sample of U.S. Workers. Am J Psychiatry 2006*b*;163:1561-1568.

Kraepelin E. Psychiatrie. Ein Lerhbuch für Studirende und Aertze. II. Band. Sechste Auflage. Verlag Barth, Leipzig, 1899.

Kraepelin, E., `Manic-depressive insanity (1921)'. In: Wolpert EA (eds.), Manic-depressive illness. International Universities Press, Inc., New York, 1977, pp. 33-111.

Krauthammer C, Klerman GL. Secondary mania: manic syndromes associated with antecedent physical illness or drugs. Arch Gen Psychiatry 1978;35:1333-1339.

Kupka RW, Luckenbaugh DA, Post RM, Suppes T, Altshuler LL, Keck PE Jr, Frye MA, Denicoff KD, Grunze H, Leverich GS, McElroy SL, Walden J, Nolen WA. Comparison of rapid-cycling and non-rapid-cycling bipolar disorder based on prospective mood ratings in 539 outpatients. Am J Psychiatry 2005;162:1273-1280.

Lam DH, Watkins ER, Hayward P, Bright J, Wright K, Kerr N, Parr-Davis G, Sham P. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. Arch Gen Psychiatry 2003;60:145-152.

Lewis L. Recognizing and meeting the needs of patients with mood disorders and comorbid illness: a consensus conference of the Depression and Bipolar Support Alliance. Biol Psychiatry 2003;54:181-183.

McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The Heritability of Bipolar Affective Disorder and the Genetic Relationship to Unipolar Depression. Arch Gen Psychiatry 2003;60:497-502.

McLeod JD, Turnbull JE, Kessler RC, Abelson JM. Sources of Discrepancy in the Comparison of a Lay-Administered Diagnostic Instrument with Clinical Diagnosis. Psychiatry Research 1990;31:145-159.

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, Kessler RC. Lifetime and 12-Month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2007;64:543-552

Miklowitz DJ, George EL, Richards JA, Simoneau TL, Suddath RL. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. Arch Gen Psychiatry 2003;60:904-912.

Miklowitz DJ. A review of Evidence-Based Psychosocial Interventions for Bipolar Disorder. J Clin Psychiatry 2006;67 (Suppl. 11):28-33.

Moreno DH, Andrade LH. The lifetime prevalence, health services utilization and risk of suicide of bipolar spectrum subjects, including subthreshold categories in the SAO Paulo ECA study. J Affect Disord 2005;87:231-241.

Nakata K, Ujike H, Sakai A, Uchida N, Nomura A, Imamura T, Katsu T, Tanaka Y, Hamamura T, Kuroda S. Association study of the brain-derived neurotrophic factor (BDNF) gene with bipolar disorder. Neurosci Lett 2003;337:17-20.

Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F, Kennedy JL. The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. Am J Hum Genet 2002;71:651-655.

Os J van, Jones P-B. Early risk factors and adult person-environment relationships in affective disorder. Psychol Med 1999;29:1055-1067.

Os J van, Park SBG, Jones P-B. Neuroticism, life events and mental health: Evidence for person-environment correlation. Br J Psychiatry 2001;178 (Suppl. 40):72-77.

Perlis RH, Brown E, Baker RW, Nierenberg AA. Clinical Features of Bipolar Depression Versus Major Depressive Disorder in Large Multicenter Trials. Am J Psychiatry 2006;163:225-231.

Perry A, Tarrier N, Morris R, McCarthy E, Limb K. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. BMJ 1999;318:149-153.

Post RM. Rubinow DR, Ballenger JC. Conditioning and sensitization in the longitudinal course of affective illness. Br J Psychiatry 1986149:191-201.

Post MR. Transduction of Psychosocial Stress Into the Neurobiology of Recurrent Affective Disorders. Am J Psychiatry 1992;149:999-1010.

Roijen L van, Essink-Bot ML, Koopmanschap MA, Bonsel G, Rutten FF. Labor and health status in economic evaluation of health care. The Health and Labor Questionnaire. Int J Technol Assess Health Care 1996;12:405-15.

Sachs GS. Strategies for improving treatment of bipolar disorder: integration of measurement and management. Acta Psychiatr Scand 2004;110 (Suppl. 422):7-17.

Schumacher J, Jamra RA, Becker T, Ohlraun S, Klopp N, Binder EB, Schulze TG, Deschner M, Schmäl C, Höfels S, Zobel A, Illig T, Propping P, Holsboer F, Rietschel M, Nother MM, Cichon S. Evidence for a Relationship Between Genetic Variants at the Brain-Derived Neurotrophic Factor (BDNF) Locus and Major Depression. Biol Psychiatry 2005;58:307-314

Schweitzer I, Maguire K, Hg CH (2005) Should bipolar disorder be viewed as manic disorder? Implications for bipolar depression. Bipolar Disord 7: 418-423

Skar P, Gabriel SB, McInnis, Bennett P, Lim Y-L, Tsan P, Schaffner S, Kirov G, Jones I, Owen M, Craddock N, DePaulo JR, Lander ES. Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential locus. Mol Psychiatry 2002;7:579-593.

Suppes T, Mintz J, McElroy SL, Altshuler LL, Kupka RW, Frye MA, Keck PE Jr, Nolen WA, Leverich GS, Grunze H, Rush AJ, Post RM. Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Foundation Bipolar Treatment Network: a sex-specific phenomenon. Arch Gen Psychiatry. 2005*a* Oct;62(10):1089-96.

Suppes T, Kelly DI, Perla JM, Challenges in the Management of Bipolar Depression. J Clin Psychiatry 2005*b*; 66 (Suppl. 5): 11-16.

Swann AC. "A two-illness model of bipolar disorder" – by RT Joffe, LT Young, GM MacQueen: a commentary. Bipolar Disord 1999;1:31-35

Szadoczky E, Papp Z, Vitrai J, Rihmer Z, Furedi J. The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. J Affect Disord 1998;50:153-162.

Vieta E. The role of third-generation anticonvulsants in the treatment of bipolar disorder. Clin Neuropsychiatry 2004;1:159-164.

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-483.

Williams JBW, Gibbon M, First MB. The Structured Clinical Interview for DSM-II-R (SCID) II: Multisite Test-Retest Reliability. Arch Gen Psychiatry 1992;49:630-636.

Wittchen HU. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. J Psychiatr Res 1994;28:57-84.

Wyatt RJ, Henter I. An economic evaluation of manic-depressive illness--1991. Soc Psychiatry Psychiatr Epidemiol 1995;30:213-219.

Summary

Bipolar disorder, or manic-depressive illness, is a mood disorder in which episodes of mania, hypomania and depression occur in alternation with intervals of normal mood. Bipolar disorder is typically a recurrent illness and may have serious consequences such as poor social and occupational functioning, impaired quality of life, hazardous behaviour that may be destructive to patients and their relatives, and a high rate of suicide. In addition to the fact that current treatment options are only partially effective in many cases, the treatment of patients with bipolar disorder is problematic due to a number of other factors: a delay in help-seeking by patients, underdiagnosing mood disorder in general practice and mental health care, and misdiagnosis of bipolar disorder as unipolar depressive disorder. Indeed, many studies have reported long delays between the onset of first symptoms of the illness and receiving the correct diagnosis and treatment. The majority of these studies were done in clinical samples, which means that the patients included suffered from a more severe form of bipolar disorder and had sought treatment. Hence, little is known about the effect of the above mentioned factors in patients in the general population, and consequently little is known of factors influencing help-seeking and receiving adequate treatment. Another point of interest is that the current concept of bipolar disorder is mainly based on studies in clinical samples, and one can question whether this reflects the true nature of mood disorder and encompasses what is often called the bipolar spectrum.

Research in the general population offers a unique opportunity to study a wider range of expressions of mood disorder, its consequences, diagnostic process and treatment history in a naturalistic setting not influenced and biased by help-seeking behaviour. In this thesis we report on four studies into the nature, prevalence and consequences of bipolar spectrum disorder as well as a study into factors influencing help-seeking and receiving treatment in the Dutch general population.

In the various studies of this thesis the following questions were addressed:

1. What is the prevalence of bipolar spectrum disorder among respondents in the general population with a diagnosis of bipolar disorder based on a fully structured interview (CIDI) when re-interviewed with a semi-structured interview (SCID) administered by clinicians? Which factors can explain the discrepancies between diagnoses based on the CIDI and the SCID? Is a possible overdiagnosis of bipolar disorder explained by the presence of a cluster B personality disorder? (chapter 2)
2. What are the disorder-related societal costs and quality of life in respondents with a bipolar spectrum disorder in the general population? (chapter 3)

3. Is there a relationship between subthreshold and clinical expressions of mood disorders over time? (chapter 4)
4. Do manic and depressive dimensions independently contribute to the use of mental health services? What is the degree of comorbidity between manic and depressive dimensions in respondents with and without mental health service use? (chapter 5)
5. What is the degree of recognition and treatment among respondents with a bipolar spectrum disorder in the general population, and what are determinants for underdiagnosis and undertreatment? (chapter 6)

In order to answer these questions we used existing data and re-interviewed participants taken from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). This is a prospective study on the prevalence of psychiatric morbidity in a representative sample of the Dutch population (N=7076) with three assessment points (1996, 1997 and 1999).

In NEMESIS, a fully structured interview (Composite International Diagnostic Interview, CIDI, Robins et al., 1998) was used. Since there is an ongoing debate about how diagnoses based on structured interviews administered by lay interviewers compare with diagnoses based on semi-structured interviews performed by clinicians, such as the Structured Clinical Interview for DSM (SCID, Spitzer et al., 1992), we performed a reappraisal study two years after the last NEMESIS assessment point. The results of this study are presented in chapter two. We re-interviewed all available NEMESIS respondents who had a CIDI/ DSM-III-R lifetime bipolar disorder at any of the three assessment points (N=74) with the SCID. In order to keep the interviewers blind for the original CIDI/DSM-III-R diagnosis, a second group of 40 randomly selected respondents who had been diagnosed with CIDI/DSM-III-R lifetime major depressive disorder was interviewed with the SCID.

The SCID distinguishes several DSM-IV subtypes of bipolar disorder: bipolar I disorder, bipolar II disorder, bipolar disorder NOS and cyclothymia. In addition a separate DSM-IV category 'mood disorder induced by substance use, specified with depressive, manic or mixed characteristics' is distinguished. Hereafter all these different disorders will be named "bipolar spectrum disorder".

Of the 74 respondents with an original diagnosis of CIDI/DSM-III-R lifetime bipolar disorder, after re-interviewing 30 respondents (40.5%) met the criteria for a SCID/DSM-IV lifetime bipolar spectrum disorder. The majority (70.5%) of the remaining 44 respondents met criteria for a SCID/DSM-IV lifetime (unipolar) depressive disorder. Of the 40 respondents with an original diagnosis of CIDI/DSM-III-R lifetime major depressive disorder, after re-interviewing 8 (20%) fulfilled the criteria for a SCID/DSM-IV lifetime bipolar spectrum disorder, and 2 respondents (5%) had developed their first

hypomanic episode in the two years between the last CIDI interview of the NEMESIS and our SCID interview. Therefore these two respondents were not included in the estimation of the prevalence based on the SCID diagnoses, but they were included in the studies described in chapter 3 and 6. Thus, after re-interviewing in total 40 respondents met criteria for a SCID/DSM-IV lifetime diagnosis of bipolar spectrum disorder: 14 respondents with bipolar I disorder, 14 with bipolar II disorder, 7 with bipolar disorder NOS, 3 with cyclothymia and 2 with bipolar disorder substance (antidepressant) induced (hereafter the latter three groups are referred to as "other bipolar disorder").

Based on the percentages of SCID/DSM-IV bipolar spectrum disorder among respondents with a CIDI/DSM-III-R bipolar disorder (1.0%; 95% CI: 0.7-1.3) or major depressive disorder (4.2%; 95% CI: 1.6-6.9), we calculated a lifetime prevalence of DSM-IV bipolar spectrum disorder of 5.2% (95% CI: 2.2-8.1), including 2% (95% CI: 0.1-4.1) for bipolar I disorder.

Interestingly, our reappraisal study showed that compared to clinical diagnoses made with the SCID, the CIDI may represent both false positive and false negative results. Discrepancies between the CIDI/DSM-III-R and SCID/DSM-IV diagnoses could not be explained by sociodemographic factors (gender and age) nor by illness characteristics such as duration of illness, number of depressive and (hypo)manic episodes, number of symptoms ever experienced during a (hypo)manic episode, comorbid SCID/DSM-IV diagnoses, comparison of single symptoms, and impairment of psychosocial functioning. Our study also showed that overdiagnosis of bipolar disorder by the CIDI/DSM-III-R could not be explained by misdiagnosis of borderline personality disorder as bipolar disorder. Finally, the differences in the minimal duration of the (hypo)manic episodes asked for (2 days in the CIDI versus 4 days in the SCID) could not account for the overdiagnosis of bipolar disorder by the CIDI (chapter 2).

Overdiagnosis and underdiagnosis of bipolar disorder by the CIDI suggest that a CIDI diagnosis may not necessarily correspond to a clinical diagnosis of bipolar disorder. At least part of this discrepancy can be explained by inconsistent reporting of episodes by respondents, which influences the comparability of the diagnostic assessments (depressive disorder versus bipolar disorder) at different times (Mc Leod et al., 1990; Haro et al., 2006). Discrepancies can also be explained by an increasing severity of symptoms (e.g., subthreshold hypomania versus syndromal hypomania) occurring in the periods between the CIDI and SCID interviews. Interviewing techniques used in the different diagnostic instruments may also play a role. In the CIDI fully structured yes or no questions are used, whereas in the SCID flexible additional open questions and conversational probing by clinicians are used (Haro et al., 2006). It can be assumed that especially for a valid diagnosis of a (hypo)manic episode with a structured interview performed by lay-interviewers, a more detailed assessment and weighing of the various (hypo)manic symptoms is necessary. Indeed in the most recent version of the CIDI,

version 3.0 (Kessler & Üstün, 2004), the symptoms of mania/hypomania are questioned in more detail and the severity of a symptom is also assessed, which resulted in better agreement between diagnoses with fully structured and semi-structured interviews (Kessler et al. 2006a). Hence we conclude that the CIDI version 3.0 and the SCID will probably result in more valid diagnoses than the CIDI version 1.1 that was used in NEMESIS.

Little is known about the costs and the impact on quality of life of bipolar disorder in the Netherlands. We therefore measured its impact on occupational functioning and self-reported quality of life, as well as the societal costs (i.e., direct costs generated by use of medical resources and indirect costs generated by productivity losses due to absence from work and reduced efficiency at work) among the respondents with a reappraised SCID/DSM-IV diagnosis of bipolar spectrum disorder (N=40). The majority of these 40 respondents (N=30, 75%) had a paying job. Compared to the general population, respondents with a SCID/DSM-IV diagnosis of bipolar spectrum disorder reported a higher number of days of absence from work (13 versus 55.5 days per year, P=0.007) and reduced efficiency at work (1.3 versus 7.7 days per year, NS), resulting in mean indirect costs of €3629 (US$3432) per respondent with a paying job per year (chapter 3). There were no significant differences in indirect costs between the various subtypes, indicating that the most severe type of bipolar disorder (bipolar I disorder) did not lead to more reduced efficiency and more days of absence than the less severe subtypes. However, this may also be partly explained by the fact that the indirect costs were based on respondents with a paying job and that only 57% of the respondents with bipolar I disorder had a paying job (compared to 85% of the respondents with bipolar II disorder and other bipolar disorder) (chapter 6).

The total mean direct costs due to medical consumption were €897 (US$848)[3] per respondent per year (chapter 3). Significantly more respondents with bipolar I disorder consulted a mental health care professional, used antipsychotics, received psychological treatment and day treatment, or were hospitalized, resulting in a significantly higher amount of direct medical costs (€1539, US$1455) than respondents with bipolar II disorder (€423, US$400, P=0.004) and other bipolar disorder (€721, US$682, P=0.038) (chapter 6). The total annual direct and indirect costs of bipolar spectrum disorder in the Netherlands based on the 5.2% prevalence were estimated at €1.94 billion (US$1.83 billion) (chapter 3).

In chapter 3 we also reported on the quality of life of respondents with a SCID/DSM-IV diagnosis of bipolar spectrum disorder, as measured with the EuroQol (Essink-Bot et al, 1993). The respondents reported a lower quality of life in comparison

3 the costs are converted from € to US$ based by the mean exchange rate for 2002 of 1€ = 0.9456 US$. The data on costs were collected in 2002

to people in the general population, although this finding did not reach statistical significance (P=0.084).

In addition, the mean score for self-perceived health status, measured with a Visual Analogue Scale (VAS, van Roijen et al., 1996), was significantly lower than the mean score in the general population (77.18 versus 84.2, P=0.013).

In chapters 4 and 5 we examined the milder expressions of mood disorders among the NEMESIS respondents who reported lifetime mood symptoms assessed by the CIDI. Although as explained earlier the comparability of CIDI/DSM-III-R and SCID/DSM-IV diagnoses of bipolar spectrum disorder appears to be limited, the use of CIDI data on lifetime mood symptoms seems justified since the CIDI is a reliable instrument with high interrater and test-retest reliability (Wittchen, 1994).

Previous studies suggest that subthreshold depression and subthreshold (hypo)mania are common phenomena although little is know about the prognosis in terms of transition to a clinical disorder. Therefore, in chapter 4 we examined the temporal relation between subthreshold and clinical expressions of mood disorder. At the first assessment point of NEMESIS the lifetime prevalences of depressive and (hypo)manic symptoms were 17.2% and 1.2%, respectively. Predictive values of mood symptoms at the first assessment point for a DSM-III-R mood disorder 1-3 years later ranged from 14.3% to 50%. (Hypo)manic mood symptoms had much higher predictive values than unipolar manifestations not only for bipolar disorder, but also for major depression. The high predictive value of (hypo)manic symptoms for mood disorders suggests that the experience of these symptoms is a stronger indicator of a vulnerability for mood disorder than the experience of depressive symptoms. Our study shows that the subthreshold expressions of depression and (hypo)mania are prevalent in the general population and are continuous with more severe clinical states over time. The cross-prediction of mood symptoms supports a continuum from depressive to (hypo)manic states.

Berkson (1946) stated that the high rates of comorbidity seen in clinical settings may in part be an artefact if the separate comorbid disorders independently influence help-seeking behaviour and need for care. Since the original concept of bipolar disorder is essentially based on observations of help-seeking individuals who have come to the attention of clinicians, the observed association between depressive and manic episodes in clinical practice may be influenced by treatment-seeking (so-called Berkson's bias). We examined in the NEMESIS population whether manic and depressive dimensions independently contributed to mental health service use, and determined the degree of comorbidity between manic and depressive dimensions in respondents with and without mental health service use. Manic and depressive dimensions indeed contributed independently to mental health service use.

Comorbidity (i.e., co-existence) of manic and depressive dimensions was significantly higher in respondents with mental health service use than in those without, both retrospectively (16.7% versus 7.1%, P=0.000) and prospectively (10.8% versus 6.6%, P=0.017). Thus, bipolar disorder consists of manic and depressive dimensions that may be much more loosely associated than (Berkson) biased clinical observations suggest. In contrast to the current concept, bipolar disorder may be seen as two separate but related disorders, mania and depression. Therefore, a dimension-specific approach may be more productive in clarifying the aetiology of mood disorder (chapter 5).

Our finding of relatively separate manic and depressive dimensions seems to contrast with the concept of a mood spectrum, as supported by the findings in chapter 4. However, pure mania and pure depression can be seen as the two extremes of one mood spectrum. Mood disorders can be conceptualised as a disease with affective dysregulation as a core feature. The clinical expression of affective dysregulation varies on a continuum from pure depressive to pure manic symptoms with different mixed states (depression with manic symptoms or mania with depressive symptoms) in between. In addition, the severity of manic and depressive symptoms varies on a continuum from normal to pathological.

In chapter 6 we studied the degree of recognition and treatment of bipolar disorder and factors that influenced recognition and treatment. Of the 40 respondents with a lifetime SCID/DSM-IV diagnosis of bipolar spectrum disorder, only 5 (12.5%) had been recognized as such by a mental health care professional and had agreed with their diagnosis. Only these 5 respondents used a mood stabilizer (lithium or an anticonvulsant) and received psychological treatment. The remaining 35 respondents (87.5%) were unaware of having bipolar disorder. Ten (25%) respondents thought they had depressive disorder, 18 (45%) another disorder and 7 (17.5%) were convinced that they had no disorder at all. The majority of our bipolar respondents had sought help from their general practitioner (N=36, 90%) and from a mental health care professional (N=25, 69.4%). Nevertheless, only 5 of them had received a correct diagnosis and adequate treatment. This will be due to factors inherent to the illness, the patient and the health care professional. The former relates to hypomanic episodes not being experienced as abnormal or not being remembered during a depressive state. Indeed, most respondents sought help for depression and did not experience their hypomanic episodes as dysfunctional but in contrast as pleasant and productive or as a normal feature of their personality. With respect to factors related to the patient (help-seeking behaviour and knowledge about the disorder) our results show that self-recognition of bipolar disorder appears to be the most important factor in receiving adequate treatment. Only those respondents who agreed with the diagnosis received adequate treatment and those who did not perceive themselves as ill sought significantly less

help. Finally, based on our results, it can be assumed that with respect to factors related to health care professionals (i.e., are they sufficiently trained to recognize this specific disorder?) bipolar disorder is not recognized adequately by both general practitioners and mental health care professionals. Interestingly, comorbidity and severity of bipolar disorder, expressed by type of bipolar disorder, number of episodes and age of onset, did not influence their recognition.

In chapter 7 we have discussed the most important findings of the current studies, their strengths and limitations, and the implications for clinical practice and future research. In our study among respondents from the general population with a CIDI/DSM-III-R diagnosis of bipolar disorder or major depressive disorder, we found a low concordance between a CIDI and a SCID diagnosis. This is probably best explained by the structured way (hypo)manic symptoms are explored (in the CIDI with yes or no questions in contrast to the open-ended and conversational probing with the SCID), inconsistent reporting of episodes by respondents (which influences the comparability of the diagnostic assessments at different times), and an increasing severity (e.g., subthreshold hypomania to syndromal hypomania) of symptoms occurring in the period between the CIDI and SCID interviews.

Based on the SCID, we found a prevalence of 5.2% of DSM-IV bipolar spectrum disorder. Despite the fact that these subjects reported impaired functioning and a lower quality of life, recognition of bipolar spectrum disorders by general practitioners and mental health care professionals was low. Although obviously not all respondents with a bipolar spectrum disorder needed treatment at the time of the interview, better detection and follow-up of subjects with milder expressions of bipolar disorder is important because these less severe expressions are a risk factor for developing episodes of full mania or depression. Our study shows that self-recognition is the most important factor in treatment seeking and receiving adequate treatment. Therefore, it is important to pay attention to awareness and acceptance of the disorder when the diagnosis of bipolar disorder is made.

Our results support the idea of a continuum from depressive to manic states with pure mania and pure depression as the two extremes of a mood spectrum as well as a continuum from normal to pathological. We conclude that a dimensional approach of symptoms represent nature better than a categorical one. Therefore, a combination of a categorical and a dimensional system would be useful for clinical practice. Although a categorical approach reflects the way clinicians think, a dimensional approach is closer to reality. Psychopathology could be described along a number of dimensions, for example high on depression, high on mania, low on psychosis and high on episode frequency.

Mood disorders can be conceptualised as disorders with affective dysregulation as a core feature. To clarify the complex aetiology of mood disorder, it may be rewarding to identify separate risk factors for manic and depressive dimensions in addition to risk factors for affective dysregulation.

Samenvatting

De bipolaire stoornis (of manisch-depressieve stoornis) is een stemmingstoornis waarin episoden van (hypo)manie (verhoogde stemming, prikkelbaarheid en overactiviteit) en depressie (verlaagde stemming en verlaagde activiteit) afgewisseld worden met episoden met normale stemming en normaal functioneren. De aandoening heeft in de meeste gevallen een terugkerend karkater en kan ernstige gevolgen hebben, zoals: verminderd sociaal en beroepsmatig functioneren, verminderde kwaliteit van leven, risicovol gedrag dat destructief kan zijn voor de patiënt en zijn naasten, en een hoog suïciderisico. De behandeling van patiënten met een bipolaire stoornis kent, naast het feit dat de huidige behandelingen in veel gevallen maar deels effectief zijn, een aantal specifieke problemen: vertraging in het hulpzoeken door patiënten, onderdiagnostiek van de bipolaire stoornis in de huisartsenpraktijk en de GGZ, en misdiagnostiek van de bipolaire stoornis als depressieve stoornis. Veel onderzoeken rapporteren dan ook een lange periode tussen de eerste symptomen van de ziekte en het stellen van de juiste diagnose. Het merendeel van deze studies zijn echter gedaan in klinische populaties, wat inhoudt dat de geïncludeerde patiënten leden aan een ernstige vorm van de bipolaire stoornis en reeds hulp hadden gezocht. Weinig is echter bekend over het effect van bovengenoemde factoren bij patiënten in de algemene bevolking en als gevolg daarvan is er weinig bekend over factoren die van invloed zijn op het zoeken van hulp en het ontvangen van de juiste behandeling. Een ander interessant aspect is dat het huidige concept van bipolaire stoornissen eveneens voornamelijk gebaseerd is op studies in klinische populaties. Dit roept de vraag op of dat concept de aard van stemmingsstoornissen juist weergeeft.

Onderzoek in de algemene bevolking biedt een unieke mogelijkheid om de uitingsvormen, de gevolgen, het diagnostische proces en de behandelgeschiedenis van bipolaire stoornissen te onderzoeken in een natuurlijke setting die niet beïnvloed is door hulpzoekgedrag.

In dit proefschrift worden vier onderzoeken beschreven naar de aard, prevalentie en gevolgen van bipolaire stoornissen in de algemene bevolking. Ook wordt een onderzoek beschreven naar factoren die van invloed zijn op het zoeken van hulp en het ontvangen van de juiste diagnose en behandeling.

In de verschillende hoofdstukken van dit proefschrift worden de volgende onderzoeksvragen behandeld:

1. Wat is de prevalentie van bipolaire spectrum stoornissen bij respondenten in de algemene bevolking met een diagnose bipolaire stoornis vastgesteld met

een volledig gestructureerd interview, het *Composite International Diagnostic Interview* (CIDI), bij herinterview met een semi-gestructureerd interview afgenomen door clinici, het *Structured Clinical Interview for DSM* (SCID)? Hoe kunnen de verschillen tussen de CIDI en SCID diagnoses verklaard worden? Is mogelijke overdiagnostiek van bipolaire stoornissen met de CIDI te verklaren door de aanwezigheid van een cluster B persoonlijkheidsstoornis? (hoofdstuk 2)

2. Wat zijn de maatschappelijke kosten als gevolg van bipolaire spectrum stoornissen en wat is de kwaliteit van leven van mensen met een bipolaire spectrum stoornis in de algemene bevolking? (hoofdstuk 3)
3. Is er een relatie tussen subsyndromale en klinische uitingsvormen van manie en depressie? (hoofdstuk 4)
4. Dragen manische en depressieve dimensies onafhankelijk van elkaar bij aan het zoeken naar hulp bij de GGZ? Wat is de mate van comorbiditeit tussen manische en depressieve dimensies bij respondenten die wel en geen hulp zochten bij de GGZ? (hoofdstuk 5)
5. In welke mate wordt bij mensen in de algemene bevolking met een bipolaire spectrum stoornis de ziekte als zodanig herkend en behandeld? Wat zijn determinanten voor onderdiagnostiek en onderbehandeling? (hoofdstuk 6)

Om deze vragen te beantwoorden hebben we gebruik gemaakt van data uit de *Netherlands Mental Health Survey and Incidence Study* (NEMESIS). Daarnaast hebben we een vervolgonderzoek uitgevoerd bij respondenten met een bipolaire stoornis in NEMESIS. NEMESIS is een prospectief onderzoek met drie meetmomenten (1996, 1997 en 1999) naar het voorkomen van psychische stoornissen in een representatieve steekproef van de Nederlandse bevolking (N=7076). Voor het vaststellen van de psychopathologie werd gebruik gemaakt van een volledig gestructureerd interview, het *Composite International Diagnostic Interview* (CIDI, Robins e.a., 1998), afgenomen door getrainde leken. De vraag is hoe de CIDI diagnoses zich verhouden tot diagnoses gebaseerd op een semi-gestructureerd interview afgenomen door een clinicus zoals het *Structured Clinical Interview for DSM* (SCID, Spitzer e.a., 1992). Daarom hebben we alle beschikbare NEMESIS respondenten met een lifetime CIDI/DSM-III-R diagnose bipolaire stoornis op één van de drie meetmomenten (N=74) ongeveer twee jaar later opnieuw geïnterviewd met de SCID. Om de interviewers blind te houden voor de oorspronkelijke CIDI diagnose werd ook een willekeurig geselecteerde controlegroep van NEMESIS respondenten met een CIDI/DSM-III-R diagnose depressieve stoornis (N=40) geïnterviewd.

De SCID stelt de volgende DMS-IV typen bipolaire stoornis vast: bipolaire I stoornis, bipolaire II stoornis, bipolaire stoornis Niet Anders Omschreven (NAO) en

cyclothymie. Daarnaast stelt de SCID de stemmingsstoornis veroorzaakt door het gebruik van een middel of een somatische aandoening, met depressieve, manische of gemengde kenmerken vast. Hierna worden al deze stoornissen samen "bipolaire spectrum stoornis" genoemd

Van de 74 respondenten met een lifetime CIDI/DSM-III-R diagnose bipolaire stoornis voldeden 30 (40.5%) respondenten aan de criteria voor een lifetime SCID/DSM-IV diagnose bipolaire spectrum stoornis. De meerderheid (70.5%) van de overige 44 respondenten voldeed aan de criteria van een lifetime SCID/DSM-IV diagnose depressieve stoornis. Van de 40 respondenten met een lifetime CIDI/DSM-III-R diagnose depressieve stoornis voldeden er 8 (20%) aan de criteria van een lifetime SCID/DSM-IV diagnose bipolaire spectrum stoornis en twee respondenten (5%) maakten hun eerste hypomanische episode door in de twee jaar tussen het laatste CIDI interview en het SCID interview. Deze twee respondenten zijn niet meegerekend in de schatting van de prevalentie gebaseerd op de SCID, maar zijn wel geïncludeerd in de studies beschreven in hoofstuk 3 en 6. In totaal voldeden dus 40 respondenten aan de criteria van een SCID/DSM-IV lifetime diagnose bipolaire spectrum stoornis: 14 respondenten met een bipolaire I stoornis, 14 met een bipolaire II stoornis, 7 met een bipolaire stoornis NAO, 3 met cyclothymie en 2 met een bipolaire stoornis door een middel (antidepressiva) geïnduceerd (de laatste drie groepen worden hierna samen "andere bipolaire stoornis" genoemd). Gebaseerd op de percentages SCID/DSM-IV bipolaire spectrum stoornis bij de respondenten met een CIDI/DSM-III-R bipolaire stoornis (1.0%; 95% BI: 0.7-1.3) of depressieve stoornis (4.2%; 95% BI: 1.6-6.9) berekenden we een lifetime prevalentie voor DSM-IV bipolaire spectrum stoornissen van 5.2% (95% BI: 2.2-8.1), inclusief 2% (95% BI: 0.1-4.1) voor de bipolaire I stoornis.

Deze studie laat zien dat de CIDI leidt tot overdiagnostiek maar ook tot onderdiagnostiek in vergelijking met de klinische diagnoses vastgesteld met de SCID. De gevonden verschillen tussen de CIDI/DSM-III-R en SCID/DSM-IV diagnoses konden niet verklaard worden door leeftijd, geslacht en ziektekenmerken zoals de duur van de ziekte, het aantal depressieve en (hypo)manische episoden, het aantal symptomen gedurende een (hypo)mane episode, comorbide SCID/DSM-IV stoornissen, vergelijking van soort symptoom en vermindering in psychosociaal functioneren. De overdiagnostiek kon ook niet verklaard worden doordat een borderline persoonlijkheidsstoornis werd aangezien voor een bipolaire stoornis door de CIDI. Evenmin verklaarde het verschil in gevraagde duur van de (hypo)manie (2 dagen in de CIDI versus 4 dagen in de SCID) de overdiagnostiek van bipolaire stoornis door de CIDI (hoofdstuk 2).

De gevonden overdiagnostiek en onderdiagnostiek van bipolaire stoornissen met de CIDI veronderstelt dat een CIDI diagnose niet noodzakelijkerwijs overeenkomt met een klinische diagnose bipolaire stoornis. Een deel van de discrepantie kan verklaard

worden door inconsistente rapportage van episoden door de respondenten wat de vergelijkbaarheid van diagnoses (depressieve stoornis versus bipolaire stoornis) op verschillende tijdstippen beïnvloedt (Mc Leod e.a., 1990; Haro e.a., 2006). Een andere verklaring voor de gevonden discrepantie kan een toename in de ernst van de symptomen zijn (subsyndromaal versus klinische hypomanie) in de periode tussen de CIDI en SCID interviews. De interviewtechnieken die gebruikt worden in de verschillende diagnostische instrumenten spelen eveneens een rol. Zo maakt de CIDI gebruik van volledig gestructureerde en gesloten vragen terwijl de SCID gebruik maakt van open vragen en het doorvragen door de clinicus stimuleert (Haro e.a., 2006). Veronderstelt kan worden dat voor een juiste beoordeling van een (hypo)manie door getrainde leken zonder klinische ervaring een gedetailleerde beoordeling van de verschillende (hypo)mane symptomen noodzakelijk is. In de meest recente versie van de CIDI (versie 3.0, Kessler & Üstün, 2004) worden de (hypo)mane symptomen inderdaad in meer detail bevraagd en wordt ook de ernst van de symptomen vastgesteld. Dit leidt tot een betere overeenstemming tussen diagnoses vastgesteld met de CIDI en de SCID (Kessler e.a., 2006a). Derhalve concluderen we dat de CIDI versie 3.0 en de SCID meer valide diagnoses geven dan de in NEMESIS gebruikte CIDI versie 1.1.

Er is weinig bekend over de kosten die bipolaire stoornissen met zich meebrengen en over de invloed van bipolaire stoornissen op de kwaliteit van leven in Nederland. Dit hebben wij onderzocht bij de respondenten met een SCID/DSM-IV diagnose bipolaire spectrum stoornis (N=40). De directe kosten als gevolg van gebruik van de gezondheidszorg en de indirecte kosten als gevolg van ziekteverzuim en verminderde productiviteit werden bepaald, evenals de kwaliteit van leven van de respondenten. Het grootste deel van de 40 respondenten (N=30, 75%) had een betaalde baan. Zij waren gemiddeld 55.5 dagen afwezig van hun werk. Dit was significant hoger (P=0.007) dan het gemiddeld aantal ziektedagen (13) in de algemene Nederlandse bevolking. De respondenten gaven aan gemiddeld 7.7 dag minder efficiënt te werken (tegenover 1.3 dag in de algemene bevolking). Dit leidt tot een gemiddelde voor de indirecte kosten van €3629 (US$3432) op jaarbasis per respondent met een betaalde baan (hoofdstuk 3). Er werden geen significante verschillen gevonden in indirecte kosten tussen de verschillende subtypes SCID/DSM-IV diagnoses. Dit suggereert dat de meest ernstige vorm, de bipolaire I stoornis, niet tot meer ziekteverzuim en verminderde efficiëntie op het werk leidde dan de minder ernstige vormen van de bipolaire stoornis. Dit kan echter gedeeltelijk verklaard worden door het feit dat de indirecte kosten gebaseerd waren op respondenten met een betaalde baan en dat maar 57% van respondenten met een SCID/DSM-IV diagnose bipolaire I stoornis een betaalde baan had (in vergelijking met 85% van de respondenten met een bipolaire II stoornis en een andere bipolaire stoornis) (hoofdstuk 6).

De gemiddelde directe kosten als gevolg van zorggebruik was €897 (US$848)[4] per jaar per respondent (hoofdstuk 3). Een significant groter aantal respondenten met een bipolaire I stoornis zocht hulp bij de GGZ, gebruikte antipsychotica, kreeg psychologische behandeling en was in dagbehandeling of werd opgenomen. Dit alles leidde tot significant hogere directe kosten (€1539, US$1455) dan bij respondenten met een bipolaire II stoornis (€423, US$400, *P*=0.004) en bij respondenten met andere bipolaire stoornis (€721, US$682, *P*=0.038) (hoofdstuk 6). De totale jaarlijkse directe en indirecte kosten van bipolaire spectrum stoornissen werd op basis van een prevalentie van 5.2% geschat op €1.94 miljard (US$1.83 miljard) (hoofdstuk 3).

In hoofdstuk 3 doen we ook verslag van de kwaliteit van leven van respondenten met een SCID/DSM-IV diagnosis bipolaire spectrum disorder, gemeten met de EuroQol (Essink-Bot et al, 1993). Respondenten meldden een, niet significante, lagere kwaliteit van leven in vergelijking met mensen in de algemene bevolking (*P*=0.084). De gemiddelde score voor de zelf-waargenomen gezondheidstoestand, gemeten met de Visual Analogue Scale (VAS, van Roijen et al., 1996), was significant lager dan de gemiddelde score in de algemene bevolking (77.18 versus 84.2, *P*=0.013).

In hoofdstuk 4 en 5 worden de mildere vormen van stemmingsstoornissen onderzocht bij de NEMESIS respondenten met door de CIDI vastgestelde lifetime stemmingssymptomen. Ofschoon de vergelijkbaarheid van CIDI/DSM-III-R en SCID/DSM-IV diagnoses bipolaire spectrum stoornissen beperkt is, is het gebruik van de CIDI data met betrekking tot de lifetime stemmingssymptomen gerechtvaardigd omdat de CIDI een betrouwbaar instrument is met een goede interbeoordelaars- en test-hertestbetrouwbaarheid (Wittchen, 1994).

Eerder onderzoek toonde aan dat subsyndromale depressie en subsyndromale (hypo)mania vaak voorkomen ofschoon er weinig bekend is over de overgang naar een klinische stoornis. In hoofdstuk 4 hebben we daarom de temporele relatie tussen subsyndromale en klinische uitingen van stemmingsstoornissen onderzocht. Op het eerste meetmoment van NEMESIS waren de lifetime prevalentie van depressieve en (hypo)manische symptomen respectievelijk 17.2% en 1.2%. De voorspellende waarden van stemmingssymptomen op het eerste meetmoment voor een DSM-III-R stemmingstoornis 1-3 jaar later varieerden van 14.3% tot 50%. (Hypo)manische symptomen hadden een veel hogere voorspellende waarde dan unipolaire manifestaties, niet alleen voor bipolaire stoornissen maar ook voor unipolaire depressieve stoornissen. De hoge voorspellende waarde van (hypo)manische symptomen voor stemmingsstoornissen duidt erop dat het ervaren van deze symptomen een sterkere

4 Voor het berekenen van de kosten van euro's naar dollars werd gebruikt gemaakt van de gemiddelde koers in 2002 (1€ = 0.9456 US$). De data voor het berekenen van de kosten werden in 2002 verzameld.

indicator is van de kwetsbaarheid voor stemmingsstoornissen dan het ervaren van depressieve symptomen. Ons onderzoek laat zien dat subsyndromale uitingen van depressieen (hypo)manie voorkomen in de algemene bevolking en dat zeeen continuüm vormen met de ernstigere klinische uitingsvormen van stemmingsstoornissen. De bevinding dat (hypo)manische symptomen een voorspeller van depressie kunnen zijn en vice versa ondersteunt het bestaan van een continuüm van depressie naar (hypo)manie.

Aangezien het oorspronkelijke concept van bipolaire stoornissen gebaseerd is op observaties van hulpzoekende individuen die onder de aandacht van clinici zijn gekomen, kan het waargenomen verband tussen depressieve en manische episoden in klinische settings beïnvloed zijn door het zoeken naar behandeling (de zogenaamde Berkson's bias). Wij onderzochten dan ook in de NEMESIS populatie of manische en depressieve dimensies onafhankelijk van elkaar bijdroegen aan het zoeken van hulp bij de GGZ en stelden de mate van comorbiditeit vast tussen manische en depressieve dimensies bij respondenten die wel en geen hulp zochten bij GGZ. Manische en depressieve dimensies droegen inderdaad onafhankelijk van elkaar bij aan het zoeken van hulp bij de GGZ. Comorbiditeit van manische en depressieve dimensies was significant hoger bij respondenten die hulp zochten bij de GGZ dan bij respondenten die dat niet deden, zowel retrospectief (16.7% versus 7.1%, P=0.000) als prospectief (10.8% versus 6.6%, P=0.017). Dit suggereert dat de bipolaire stoornis bestaat uit manische en depressieve dimensies die minder sterk met elkaar geassocieerd zijn dan de (Berkson-biased) klinische observaties doen vermoeden. In tegenstelling tot het huidige concept, kan de bipolaire stoornis misschien beter gezien worden als twee aparte maar wel gerelateerde stoornissen, de manie en de depressie. Daarom kan een dimensie-specifieke benadering productiever zijn bij het verhelderen van de etiologie van stemmingsstoornissen (hoofdstuk 5).

Onze bevinding van relatief losstaande manische en depressieve dimensies, lijkt het concept van een stemmingscontinuüm, zoals ondersteunt door de bevindingen in hoofdstuk 4, tegen te spreken. Manie en depressie kunnen echter beschouwd worden als de twee uiteinden van het stemmingscontinuüm. Stemmingsstoornissen kunnen geconceptualiseerd worden als een stoornis met affectieve dysregulatie als kerneigenschap. De klinische uiting van affectieve dysregulatie varieert op dat continuüm van zuiver depressieve tot zuiver manische symptomen met daartussen verschillende gemengde staten (depressie met manische symptomen of manie met depressieve symptomen). Daarnaast varieert de ernst van manische en depressieve symptomen in een continuüm van normaal tot pathologisch.

In hoofdstuk 6 onderzoeken we de mate van herkenning en behandeling van bipolaire spectrum stoornissen en factoren die de herkenning en behandeling beïnvloeden. Van de 40 respondenten met een lifetime SCID/DSM-IV diagnose bipolaire spectrum stoornis, waren slechts 5 (12.5%) als zodanig herkend door de GGZ en werd die diagnose door de respondent beaamd. Alleen deze 5 respondenten gebruikten stemmingsstabilisatoren (lithium of een anti-epilepticum) en kregen psychiatrische begeleiding en/of psychologische behandeling. De overige 35 respondenten (87.5%) waren zich er niet van bewust dat zij aan een bipolaire stoornis leden. Tien respondenten (25%) dachten aan een depressieve stoornis te lijden, 18 (45%) aan een andere stoornis en 7 respondenten (17.5%) waren ervan overtuigd geen enkele stoornis te hebben. De meeste van onze bipolaire respondenten hadden hulp gezocht bij de huisarts (N=36, 90%) en bij de GGZ (N=25, 69.4%). Niettemin hadden slechts 5 van hen de juiste diagnose en behandeling gekregen. Dit hangt samen met factoren die inherent zijn aan de ziekte zelf, aan de patiënt en aan de hulpverleners. Het eerste heeft te maken met het feit dat hypomane episoden niet als abnormaal worden ervaren, danwel dat ze niet worden herinnerd gedurende een depressie. De meeste respondenten zochten inderdaad hulp voor een depressie en ervoeren de hypomane episoden niet als disfunctioneel: ze ervoeren de hypomane perioden als aangenaam en productief, of als een normale kenmerk van hun persoonlijkheid. Met betrekking tot factoren inherent aan de patiënt (hulpzoekgedrag en kennis over de stoornis), laten onze resultaten zien dat erkenning en acceptatie van de bipolaire stoornis door de respondent zelf de belangrijkste factor blijkt te zijn voor adequate behandeling. Slechts die respondenten die het eens waren met de gestelde diagnose kregen een adequate behandeling, terwijl de respondenten die dachten niet aan een stoornis te leiden significant minder hulp zochten. Gebaseerd op onze resultaten kunnen we tenslotte aannemen dat met betrekking tot factoren gerelateerd aan de hulpverleners (d.w.z. zijn ze voldoende opgeleid om deze specifieke stoornis te herkennen?) bipolaire stoornissen niet adequaat herkend worden door huisartsen noch door de GGZ. Het is interessant om op te merken dat comorbiditeit en ernst van de bipolaire stoornis, zoals uitgedrukt door het type bipolaire stoornis, alsmede het aantal episoden en de beginleeftijd van de ziekte, de herkenning ervan niet beïnvloedden.

In hoofdstuk 7 worden de belangrijkste bevindingen van de huidige studies besproken. Daarin worden de sterke punten en de beperkingen van de studies en de implicaties voor de klinische praktijk en toekomstig onderzoek besproken. In onze studie bij respondenten in de algemene bevolking met een CIDI/DSM-III-R diagnose bipolaire stoornis of depressieve stoornis, vonden wij een lage concordantie tussen de CIDI en de SCID diagnoses. Dit kunnen we het beste verklaren door de manier waarop de (hypo)manische symptomen worden uitgevraagd (in de CIDI met gesloten vragen

en in de SCID met open vragen en de mogelijkheid tot doorvragen), inconsistente rapportage door respondenten (waardoor de vergelijkbaarheid van de diagnoses op de verschillende tijdstippen beïnvloed wordt), en toename in ernst van de symptomen (bijvoorbeeld subsyndromale hypomanie versus klinische hypomanie) die optrad in de periode tussen de CIDI en de SCID interviews.

Op basis van de SCID vonden wij een lifetime prevalentie van 5.2% voor bipolaire spectrum stoornissen. Ondanks het feit dat deze respondenten melding maakten van slechter functioneren en een verminderde kwaliteit van leven, was herkenning van de bipolaire spectrum stoornis door huisartsen en de GGZ laag. Ofschoon niet alle respondenten met een bipolaire spectrum stoornis ten tijde van het interview behandeling nodig hadden, is een betere herkenning en follow-up van patiënten met een milde vorm van de bipolaire stoornis belangrijk omdat deze minder ernstige uitingen een risicofactor zijn voor het ontwikkelen van een ernstigere vorm van de bipolaire stoornis. Onze studie laat zien dat erkenning en acceptatie van de stoornis door de patiënt zelf de belangrijkste factor is bij het zoeken van hulp en het krijgen van een adequate behandeling. Het is daarom belangrijk om aandacht te besteden aan de acceptatie van de stoornis en kennis over de ziekte wanneer de diagnose bipolaire stoornis wordt gesteld.

Onze resultaten ondersteunen het idee van een continuüm van depressie naar manie met zuiver manische symptomen en zuiver depressieve symptomen als de twee uiteinden van het stemmingscontinuüm. Daarnaast ondersteunen onze resultaten een continuüm van ernst waarbij manische en depressieve symptomen varieren van normaal tot pathologisch

Wij concluderen dat een dimensionale benadering van symptomen de aard van stemmingsstoornissen beter weergeeft dan een categoriale benadering. Hoewel een categoriale benadering weergeeft hoe een clinicus denkt, ligt een dimensionale benadering dichter bij de realiteit. Daarom zou een combinatie van een categoriaal en een dimensionaal systeem nuttig zijn voor de klinische praktijk. Psychopathologie kan dan aan de hand van een aantal dimensies beschreven worden, bijvoorbeeld: een hoge score voor depressie, een hoge score voor manie, een lage score voor psychose en een hoge score voor het aantal episoden.

Stemmingsstoornissen kunnen geconceptualiseerd worden als stoornissen met affectieve dysregulatie als kerneigenschap. Om de complexe etiologie van stemmingsstoornissen te verhelderen kan het lonen om te zoeken naar aparte risicofactoren voor manie en depressie en naar risicofactoren voor affectieve dysregulatie.

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Curriculum Vitae

Eline Regeer is geboren op 4 juli 1970 te Moerkapelle. Na het behalen van haar VWO-diploma volgde zij gedurende 1 jaar de opleiding tot fysiotherapeut aan de Hogeschool van Amsterdam In 1989 startte zij met de studie geneeskunde aan de Universiteit van Amsterdam. Na het afronden van de doctoraalfase volgde zij de studie Wetenschapsdynamica aan dezelfde universiteit. Zij schreef haar afstudeerscriptie over de invloed van de eugeneticabeweging op het ontstaan van de discipline genetica en behaalde in 1995 haar tweede doctoraal. In 1997 rondde zij haar medische opleiding af waarna zij als arts-assistent neurologie in het Medisch Centrum Alkmaar werkte en ervaring op deed in psychiatrisch ziekenhuis Duin en Bosch in Castricum. In april 2001 begon zij aan de opleiding tot psychiater bij Altrecht, instelling voor geestelijke gezondheidszorg in Utrecht (opleiders dr. J.M. Havenaar en dr. R.W. Kupka). In hetzelfde jaar startte zij met haar onderzoek naar de prevalentie, kosten, herkenning en behandeling van de bipolaire stoornis in de algemene bevolking in Nederland onder begeleiding van prof. dr. W.A. Nolen. Zij rondde haar opleiding tot psychiater af in augustus 2006 en sindsdien is zij werkzaam bij Altrecht op de unit voor besloten vervolgbehandeling van het Willem Arntsz huis en het behandelcentrum bipolaire stoornissen.
Eline is getrouwd met Rafael Fischer en in maart 2008 verwachten zij hun eerste kind.